VOLUME 53 NUMBER 2 FEBRUARY 1960

PROCEEDINGS

of the

ROYAL SOCIETY OF MEDICINE

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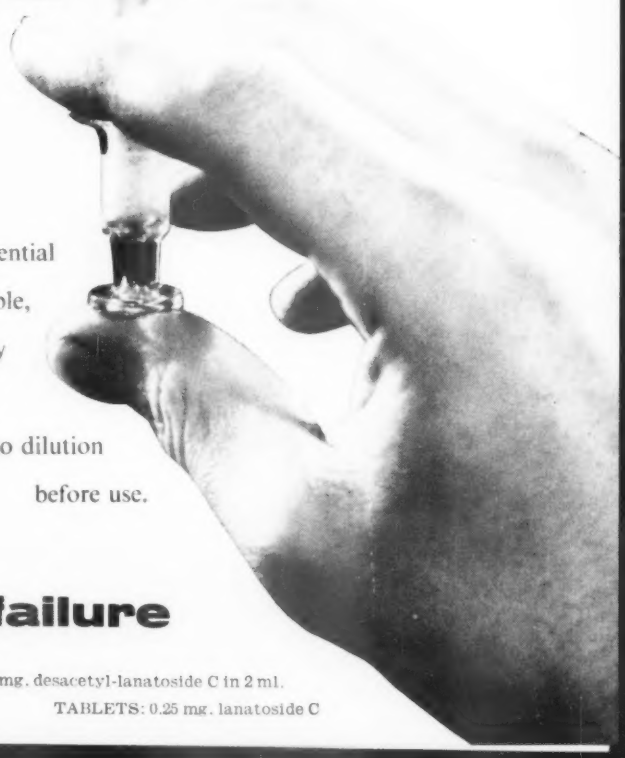

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VOLUME 53 NUMBER 2 FEBRUARY 1960

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ROYAL SOCIETY OF MEDICINE

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Vol. 53 No. 2 February 1960

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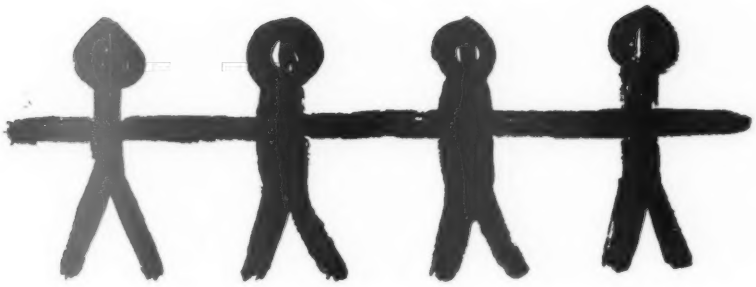
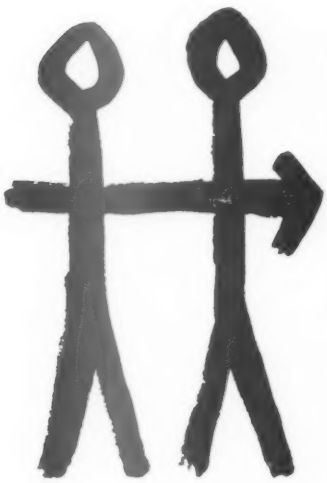


10 unknown diabetics in every GP's care...



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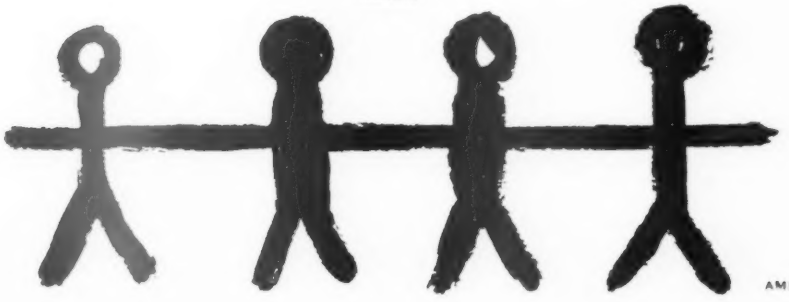

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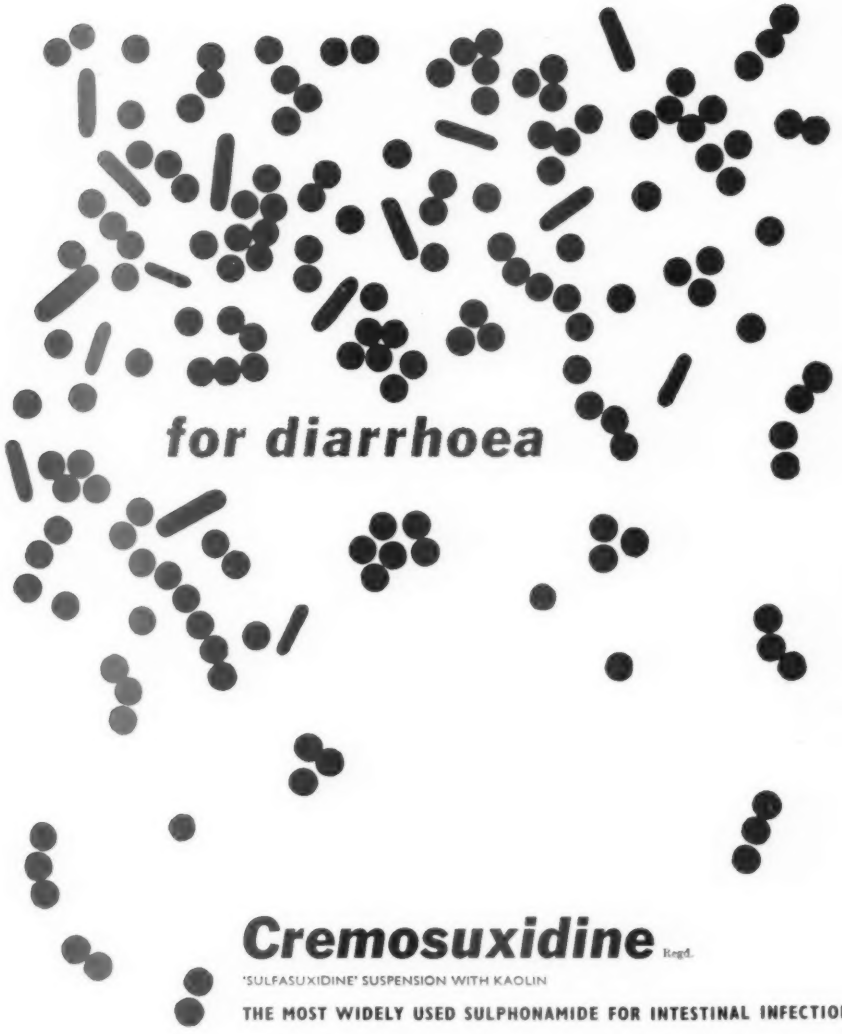

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"BARBITURATE DEATHS INCREASING"

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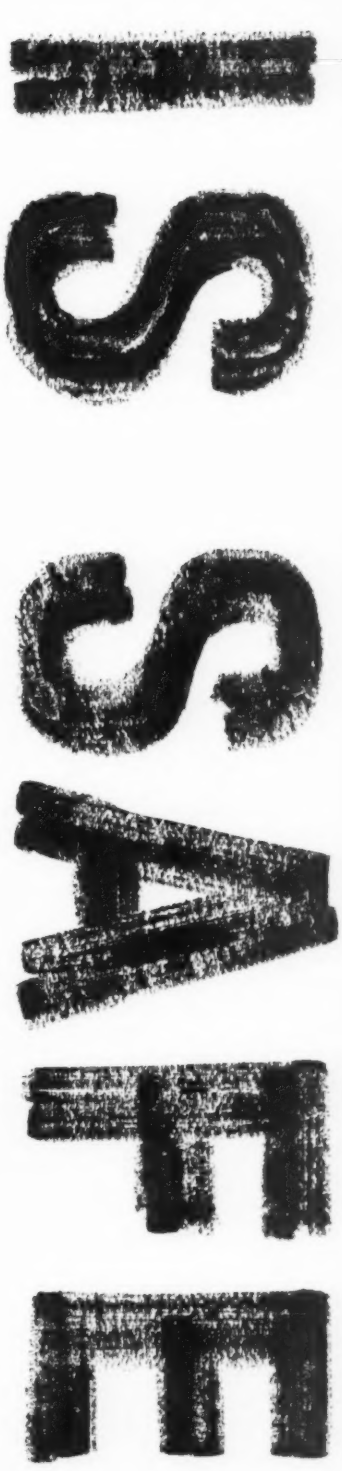
Since the introduction of 'Distaval' two years ago a number of reports have been received of cases of gross overdosing with similarly harmless results. On the other hand, no severe toxic effects of any kind have been reported.



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Proceedings of the Royal Society of Medicine Vol. 53 71

Section of Experimental Medicine and Therapeutics

President—Professor W. D. M. PATON, D.M., F.R.S.

Meeting
October 22, 1959

WALTER ERNEST DIXON MEMORIAL LECTURE

[Number 9]

Biochemical Aspects of Ketosis

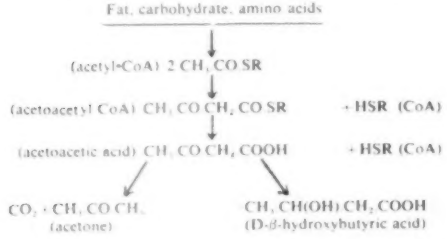
By Sir HANS KREBS, M.D., F.R.S.
Oxford

I PROPOSE to discuss the concept that the accumulation of ketone bodies arises from an inability of the liver to regulate the relative rates of certain metabolic processes. According to this concept, ketosis is a disorder of the regulation of metabolic processes rather than an insufficiency of certain enzymes or of key metabolites.

The Origin of Ketone Bodies

The bulk of the ketone bodies arises by condensation of acetate which reacts in the form of acetyl coenzyme A (CoA) (*see* Scheme 1). Two

SCHEME 1.*—PATHWAY OF FORMATION OF KETONE BODIES



*Another pathway leading from acetoacetyl CoA to free acetoacetate has been found by Lynen *et al.* (1958). This involves a reaction between acetoacetyl CoA and acetyl CoA leading to β-hydroxy-β-methylglutaryl CoA which is subsequently hydrolysed to free acetoacetic acid and acetyl CoA. It is not yet possible to assess the relative quantitative importance of the two pathways.

molecules of acetyl coenzyme A first form acetoacetyl coenzyme A and this is hydrolysed by a specific enzyme—acetoacetyl-coenzyme A deacylase. This enzyme is present in liver but absent from most other tissues (Mahler, 1953) which accounts for the fact that liver is the main site of ketone body formation.

All foodstuffs—fats as well as carbohydrates and proteins—yield acetyl coenzyme A in the course of their combustion and are therefore potential sources of ketone bodies. However, in the intact organism, the fate of acetyl coenzyme A depends partly on its origin. Only the acetyl coenzyme A derived from fatty acids with even carbon numbers and the three "ketogenic" amino acids—leucine, phenylalanine and tyrosine—produce major quantities of ketone bodies, and long-chain fatty acids rarely form more than one molecule of ketone body per molecule (Magnus-Levy, 1899, 1901, 1925). Whilst the acetyl coenzyme A arising from most sources undergoes complete oxidation through the tricarboxylic acid cycle (except for a relatively small fraction which is utilized for various synthetic processes), some of the acetyl coenzyme A arising from fatty acids and from the ketogenic amino acids can yield ketone bodies.

Site of Formation and Utilization of Ketone Bodies

The liver is by far the most important site of ketone body formation though small quantities can be formed in other tissues, e.g. kidney (Weinhouse and Millington, 1951; Jowett and Quastel, 1935). In ruminants, the wall of the rumen is an additional major source (Pennington, 1952; Hird and Symons, 1959) and, in the lactating animals, ketone bodies can also be formed by the mammary gland (Terner, 1958).

Many tissues are capable of utilizing ketone bodies as a substrate of respiration and of oxidizing them completely to carbon dioxide and water (Stadie *et al.*, 1940; Shipley, 1944; Krebs and Eggleston, 1948). This applies in particular to the mammalian heart which appears to use

acetoacetate in preference to most other substrates of oxidation (Kulka, 1958; Williamson, 1959).

Accumulation of Ketone Bodies

It is relevant to the problem of the nature of ketosis that there are many physiological or semi-physiological conditions which can be associated with an accumulation of ketone bodies above the normal level in blood and urine. These include starvation, diets low in carbohydrate (fat-protein diets, Deuel *et al.*, 1932), severe muscular exertion —"post-exercise ketosis" (Courtice and Douglas, 1936; Courtice *et al.*, 1939; Passmore and Johnson, 1958; Drury *et al.*, 1941; Gemmill, 1940), exposure to a cold environment (Sargent *et al.*, 1958), alkalosis due to hyperventilation (Davies *et al.*, 1920) or to a dose of sodium bicarbonate (Deuel *et al.*, 1935), and anæsthesia (F. L. Engel and M. G. Engel, 1958).

Some of the pathological conditions which can lead to ketosis of varying degrees have a common basis: the failure to utilize carbohydrate at the normal rate. This applies to all forms of diabetes—diabetes mellitus, diabetes due to depancreatization or to alloxan poisoning (Lukens, 1948), or to phlorizin poisoning (Goldfarb *et al.*, 1934)—to glycogen storage disease, and probably also to ketosis following vomiting (hyperemesis gravidarum and periodic vomiting of children), and to the ketosis accompanying pregnancy toxæmia of sheep.

The ketosis of lactating cows, first described in Holland in 1923 by Sjollema and Van Der Zande, though not fatal, may seriously reduce milk production and is a disease of major economic importance.

Experimentally, ketosis can be produced both in the intact body and in isolated liver preparations by substances which lower the oxaloacetate level in tissues. Examples are malonate (Recknagel and Potter, 1951), fluoroacetate (Cole *et al.*, 1955), fluorocitrate (Gal *et al.*, 1954), mesoxalate and tartronate (Edson, 1936; Krebs and Stickland, 1958. One of the most interesting forms of experimental ketosis is that produced by anterior pituitary extracts (Bennett *et al.*, 1948). The ketogenic effect of the anterior pituitary is suppressed by cortisone, hydrocortisone and related substances (Engel, 1957; M. G. Engel and F. L. Engel, 1958). These effects indicate that the metabolism of ketone bodies is under hormonal control.

Relations Between Carbohydrate and Fat Metabolism

The elucidation of intermediary stages of the oxidation of fat has made it possible to re-examine the meaning of the old remark (Rosenfeld, 1885, 1906) that "fats burn in the fire of carbohydrate", a statement circumscribing the fact that ketone bodies are mainly derived from fat, and do not accumulate when carbohydrate is burned.

Fatty acids are known to be oxidized by β-oxidation to acetyl coenzyme A; this condenses with oxaloacetate to enter the tricarboxylic acid cycle, one turn of which represents the complete oxidation of one acetate equivalent. Oxaloacetate is thus necessary for the complete oxidation of fatty acids. It cannot be formed from fatty acids but it can be synthesized from carbohydrate. Thus the need for oxaloacetate represents a link between fat and carbohydrate metabolism, even though carbohydrate is not the only source of oxaloacetate: propionate and certain amino acids—especially those which have long been recognized as glucogenic amino acids (aspartate, glutamate, proline, arginine)—can also serve as precursors of oxaloacetate. The various reactions which can yield oxaloacetate in the animal body are listed in Table I.

TABLE I.—MAIN SOURCES OF OXALOACETATE IN THE ANIMAL BODY

(1) *Carbohydrate*

Carbohydrate —(glycolysis)→ phosphopyruvate —+CO_2 + ADP→ oxaloacetate + ATP

Lactate → pyruvate —+CO_2 + TPN_{red}→ malate → oxaloacetate

Carbohydrate —rumen fermentation→ propionate —+CO_2 + CoA→ methyl malonyl CoA → succinate —oxidation→ oxaloacetate

(2) *Amino acids*

Aspartate —transamination→ oxaloacetate

Glutamate —transamination→ α-ketoglutarate —oxidation→ oxaloacetate

Proline, Arginine → glutamate —transamination→ α-ketoglutarate —oxidation→ oxaloacetate

The Role of Oxaloacetate in Ketosis

It has been suggested that ketosis arises from lack of oxaloacetate. However, the experimental tests show that this is not true for most forms of ketosis. The oxaloacetate levels in the livers of well-fed and starved rats were found by Kalnitsky and Tapley (1958) to be identical after twenty-four hours although the acetoacetate level had increased over tenfold (*see* Table II). These findings indicate that the ketosis of starvation is not due to lack of oxaloacetate. Similarly, the oxaloacetate levels of the livers of normal and alloxan-diabetic rats were equal whilst the acetoacetate levels were seven times higher in the diabetic rat. Thus the ketosis of alloxan diabetes cannot be due to lack of oxaloacetate either.

TABLE II.—OXALOACETATE AND ACETOACETATE LEVELS IN RAT LIVER

	Average values	
	Oxaloacetate (μmole/100 g fresh weight)	Acetoacetate (μmole/100 g fresh weight)
Series 1 (Kalnitsky and Tapley, 1958)		
Liver, well-fed	1·0	1·5
Liver, fasting 24 hours	1·1	15·2
Series 2 (Shaw and Tapley, 1958)		
Liver, normal	0·9	0·4
Liver, alloxan diabetes	1·0	2·8

Another way of testing the role of oxaloacetate in ketogenesis is the administration of oxaloacetate or its precursors to the ketotic organism. Experiments on various animals show that the dietary ketonuria produced by feeding butyrate is greatly reduced by the administration of oxaloacetate or its precursors (Beatty and West, 1951; Fasella *et al.*, 1958). The ketosis of alloxan-diabetic animals (Beatty and West, 1955) or of human diabetics (MacKay *et al.*, 1939; Dunlop and Arnott, 1937; Lawrence, 1937; Dibold *et al.*, 1937) or of cows suffering from bovine ketosis on the other hand, is not appreciably influenced by oxaloacetate and its precursors. Some authors (Fasella *et al.*, 1958) have drawn the conclusion from these findings that the mechanisms responsible for diabetic and dietary ketosis are "fundamentally different". I prefer to express this difference by the statement that different factors limit the formation and the utilization of acetyl coenzyme A in dietary ketosis on the one hand, and diabetic ketosis on the other.

That lack of oxaloacetate can be a cause of an accumulation of ketone bodies can be shown *in vitro* with liver preparations. As Lehninger (1946) has shown, liver mitochondria convert octanoic acid almost quantitatively to acetoacetate when added as the sole substrate, but when oxaloacetate is available some of the octanoate is converted to the acids of the tricarboxylic acid cycle or completely oxidized. The importance of oxaloacetate in ketone body accumulation can also be demonstrated in a preparation of washed liver particles suspended in saline. On addition of pyruvate, varying amounts of acetoacetate, tricarboxylic acid cycle intermediates and CO_2 are formed. The yield of acetoacetate from pyruvate is substantially increased by a variety of agents, which in different ways all reduce the supply of oxaloacetate. Malonate, oxalate, tartronate, mesoxalate, fluoromalate, fluorocitrate, and ammonium chloride are examples. Their ketogenic action is shown in Table III. Malonate prevents the formation of oxaloacetate mainly by inhibiting succinic dehydrogenase. Ammonium chloride interferes with the tricarboxylic acid cycle at the stage of α-oxoglutarate by causing its conversion to glutamate and glutamine. Most of the other agents inhibit the synthesis of C_4-dicarboxylic acids from pyruvate and CO_2.

The determination of the level of oxaloacetate in the presence of various inhibitors directly shows the reduced steady state level of oxaloacetate on addition of the ketogenic agents (Table IV). Fumarate, on the other hand, raises the

TABLE III.—EFFECT OF VARIOUS INHIBITORS ON ACETOACETATE FORMATION BY LIVER PARTICLES IN THE PRESENCE OF PYRUVATE

(0·02 M pyruvate; 30° C; 60 min; 4 ml suspension)

Additions (other than pyruvate)	Pigeon liver (22·1 mg dry weight)		Rat liver (35·0 mg dry weight)	
	O_2 (μmoles)	acetoacetate (μmoles)	O_2 (μmoles)	acetoacetate (μmoles)
None	−29·1	+ 6·5	−26·2	+ 2·7
Malonate (5×10^{-3}M)	−19·8	+ 9·4	−19·8	+ 8·8
Tartronate (10^{-2}M)	−14·6	+12·0	−21·5	+10·8
Mesoxalate (5×10^{-3}M)	−12·7	+13·9	− 7·3	+ 7·5
Oxalate (10^{-2}M)	−20·0	+12·2	−16·3	+10·4
Fluoromalate (5×10^{-4}M)	−13·6	+12·4	−11·8	+ 8·0
Fluorocitrate (10^{-4}M)	−31·6	+ 7·9	−16·8	+10·4
NH_4Cl (5×10^{-2}M)	−25·4	+ 8·2	−27·1	+ 6·5

TABLE IV.—OXALOACETATE LEVEL IN PIGEON LIVER PARTICLE SUSPENSIONS IN THE PRESENCE OF KETOGENIC SUBSTANCES

The data refer to μmoles in 8 ml suspension; 0·02 M pyruvate; 30°C; 60 min; 32·6 mg dry weight.

Additions (other than pyruvate)	None	Fluoromalate (5×10^{-4}M)	Oxalate (10^{-4}M)	Fluorocitrate (10^{-4}M)
O_2 used	−39·4	−23·0	−23·2	−21·0
Acetoacetate formed	+11·6	+21·4	+20·1	+21·0
Oxaloacetate present at end of experiment	0·12	0·06	0·07	0·05

oxaloacetate level and substantially reduces the accumulation of acetoacetate in the presence of pyruvate (Table V).

TABLE V.—EFFECT OF FUMARATE ON THE FORMATION OF ACETOACETATE AND ON THE LEVEL OF OXALOACETATE IN PIGEON LIVER PARTICLES INCUBATED WITH PYRUVATE

The data refer to μmoles in 8 ml suspension; 30°C; 60 min.

Substrates added	Pyruvate (0·02 M)	Fumarate (0·02 M)	Pyruvate (0·02 M) fumarate (0·02 M)
O_2 used	−42·7	−25·7	−47·1
Acetoacetate formed	+17·6	+ 0·5	+ 7·6
Oxaloacetate present at end of experiment	0·15	0·41	0·21

Thus the supply of oxaloacetate can be a factor controlling ketone body formation, i.e. the fate of acetyl coenzyme A. But from what has already been said about the failure of oxaloacetate to relieve some forms of ketosis, it is not the only limiting factor in ketone body accumulation.

The Role of Coenzyme A Transferase in Ketosis

It might be thought that apart from oxaloacetate derived from carbohydrate, there is also a link between fat and carbohydrate metabolism at the level of ketone body utilization. The most important reaction in animal tissues which initiates the disposal of free ketone bodies is probably that catalysed by coenzyme A transferase (Stern *et al.*, 1956). This enzyme converts acetoacetate to its reactive form, e.g. acetoacetyl CoA:

succinyl CoA + acetoacetate ⟶ succinate + acetoacetyl CoA.

However, the supply of succinyl CoA is not dependent on carbohydrate; it arises as an intermediate in the tricarboxylic acid cycle at the rate of 2 molecules per molecule of acetoacetate. It is self-generating and therefore cannot be expected to be a factor limiting the oxidative disposal of acetoacetate.

Control of Substrate Utilization as a Factor in Ketosis

There is, then, no evidence of a simple stoichiometric link between fatty acid and carbohydrate metabolism, in the form of an enzymic reaction involving one reactant derived from carbohydrate and another one derived from fat, such as earlier authors (Shaffer, 1921; Henze, 1930; Stöhr and Henze, 1932) had visualized. Yet that there is a further link between the metabolism of carbohydrate and fat is evident from the fact that when both are available they are not oxidized independently of one another. The body as a whole, and many individual tissues, burn carbohydrate in preference to fat, and fat takes the place of carbohydrate as a fuel when the supply of carbohydrate is exhausted. The total energy supply remains approximately constant, irrespective of the nature of the fuel burned. The "sparing" effect of carbohydrate on the oxidation of fat may also be expressed by the statement that carbohydrate prevents the oxidation of fat.

This competition between different substrates as fuels of respiration is shown by the following experiment in which various substrates were added to pigeon liver homogenate and the oxygen uptake, as well as some of the substrate changes, was measured (Table VI). Addition of sub-

TABLE VI.—OXIDATIVE METABOLISM OF PIGEON LIVER HOMOGENATES IN THE PRESENCE OF DIFFERENT SUBSTRATES

(The data refer to 8 ml liver homogenate containing 91·8 mg dry weight tissue. 30°C. 60 min O_2; substrates 0·01 M. The homogenates were prepared in the apparatus of Potter and Elvehjem from a mixture of 4 g of minced liver in 20 ml 0·9% KCl at 0°C. Each cup contained 2 ml of this homogenate, 1 ml 0·1 M sodium phosphate buffer of pH 7·4, 0·4 ml 0·155 M $KHCO_3$, 0·4 ml 0·02 M $MgCl_2$, 0·4 ml 0·02 M sodium ATP, 0·4 ml 0·2 M substrate solution (sodium salt) and sufficient 1·15% KCl to make up 8 ml)

Substrates added: Metabolic changes (μmoles)	None	Citrate	α-Oxoglutarate	Succinate	Fumarate
O_2	−54·5	−48·0	−54·8	−73·8	−54·8
Citrate	0	−34·0	+ 0·4	+ 3·0	+ 5·3
Malate + fumarate	0	+ 5·1	+26·6	+39·0	−52·5
α-Oxoglutarate	0	+29·0	−41·1	+ 5·9	+14·4
Succinate	0	+ 1·4	+ 6·0	−61·6	0
Pyruvate	0	+ 4·2	+10·3	+ 9·0	+ 9·8

TABLE VII.—OXIDATIVE METABOLISM OF WASHED PIGEON LIVER PARTICLES IN THE PRESENCE OF DIFFERENT SUBSTRATES

Washed pigeon liver particles, 8 ml suspension in saline medium (47·0 mg dry weight). 30° C. 60 min O_2. Medium: 1 ml 0·1 M Na-phosphate buffer pH 7·4; 0·4 ml 0·02 M $MgCl_2$; 0·4 ml 0·155 M $KHCO_3$; 0·4 ml 0·02 M ATP; 2 ml washed particles in 1·15% KCl; substrate solution 0·2 M (0·8 or 0·4 ml); 1·15% KCl to 8 ml.

Substrates added:	None	Pyruvate (0·02 M)	Citrate (0·01 M)	α-Oxoglutarate (0·01 M)	Fumarate (0·01 M)
Metabolic changes (μmoles)					
O_2	−6·7	−71·3	−43·0	−48·1	−56·0
Pyruvate	0	−117	+ 2·4	+ 4·4	+ 2·7
Acetoacetate ..	+2·7	+ 12·5	+ 1·4	+ 0·7	+ 1·3
Citrate	0	+ 11·2	−37·0	+ 1·6	+ 2·8
α-Oxoglutarate ..	+0·8	+ 11·9	+16·0	−20·6	+ 7·5
Malate + fumarate	0	+ 17·6	+ 1·8	+ 11·6	−54·2

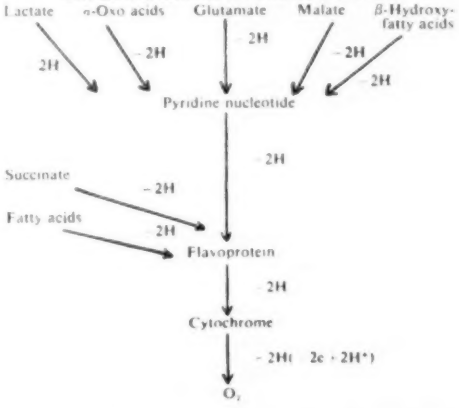
strates did not affect the rate of oxygen consumption very much except in the case of succinate, which caused a substantial increase. In contrast, the substrate changes were greatly affected by the additions. When no substrate was added, endogenous material served as a fuel and no intermediates accumulated. The data for the removal of the added substrates indicate that the added material largely replaced the endogenous material as a fuel. Thus, in the presence of citrate, about 30% of the oxygen consumption was due to the conversion of citrate to α-oxoglutarate, about 3% to the formation of succinate, about 16% to the formation of malate and fumarate, and about 17% to the formation of pyruvate. When α-oxoglutarate was added, the main oxidative reactions were the conversion of the substrate to succinate (5·5%), to malate and fumarate (48·5%) and to pyruvate (28%). In the presence of succinate, the conversion of succinate to fumarate and malate accounted for 26·5% of the oxygen consumption. With fumarate as a substrate, most of the oxygen consumption was due to the stages of the tricarboxylic acid cycle between fumarate and α-oxoglutarate.

Similar data were obtained with washed liver particles (Table VII). Again, the main metabolic reactions were those stages of the cycle nearest to the added substrate. In the case of pyruvate, this was the conversion of pyruvate to acetyl coenzyme A.

In these experiments, the high concentration of the added substrate was no doubt an important factor in displacing other oxidizable materials as fuels of respiration. How the mechanisms operate which regulate the choice of substrate is by no means fully known, but it can be explained in general terms why the available nutrients are not simultaneously burned.

A major factor is the circumstance that all oxidations involve the same co-factors and are therefore not entirely independent processes. The transport of hydrogen from a substrate to molecular oxygen generally involves three types of catalysts which are arranged in series. They are the pyridine nucleotides, flavoproteins and iron-porphyrins and only the first step of the transport chain varies from substrate to substrate. This is shown diagrammatically in Scheme 2.

SCHEME 2.—JOINT PATHWAYS OF HYDROGEN TRANSPORT FROM DIFFERENT SUBSTRATES TO MOLECULAR OXYGEN



Choice of substrate thus means competition of several substances for the same catalyst.

Over-production or Under-utilization of Acetyl Coenzyme A

The concept of substrate competition suggests that ketosis may be a condition where the balance of substrate utilization is disturbed. Ever since it has been appreciated that ketone bodies can be normal intermediates of metabolism it has been realized that the accumulation of ketone bodies could be due either to over-production or to under-utilization. In the light of present knowledge, this means over-production or under-utilization of acetyl coenzyme A. If the

utilization of acetyl coenzyme A through the tricarboxylic acid cycle is impeded, then any excess, instead of undergoing oxidation, would be expected to be shunted in the liver to the synthesis of ketone bodies. On the other hand, an over-production would mean that more acetyl coenzyme A is formed than is needed for energy release and this excess would again be expected to be shunted to the synthesis of ketone bodies.

There is no evidence of under-utilization of acetyl coenzyme A in the ketotic organism, in the sense of the reduced rate of the tricarboxylic acid cycle. The capacity of the body as a whole to burn acetate is never fully used in a resting organism. On exercise, the total energy supply may be trebled and of this increase about two-thirds is due to the oxidation of acetate. It is true that the differences in respiration between the resting and maximally active tissue are small in liver (where most of the ketone bodies are produced) but numerous measurements of the respiration of liver preparations *in vitro* have shown that the rate of respiration, in terms of Q_{O_2}, is not depressed in starvation, although the rate of ketone body accumulation may rise four-fold (e.g. Edson, 1935, *see* Table VIII). It is thus

TABLE VIII.—COMPARISON OF RATES OF RESPIRATION AND OF ACETOACETATE FORMATION IN THE LIVER OF STARVED AND WELL-FED RATS

Average values (Edson, 1935)

	Q_{O_2}	$Q_{Acetoacetate}$
Well-fed liver ..	−11·5	+0·33
Starved (24 h) liver .	−10·6	+1·34

clear that ketosis can occur whilst the total oxidative capacity of the liver and the rate of utilization of acetyl coenzyme A through the tricarboxylic acid cycle are normal.

This indicates that ketone body accumulation is not due to under-utilization, but to over-production of acetyl coenzyme A, and raises the question of why over-production occurs.

Accumulation of Intermediary Metabolites

An over-production of intermediary metabolites and their accumulation is a most exceptional event in animal tissues. The non-accumulation indicates that intermediates when available react in preference to the starting material. A substrate molecule of respiration, once its oxidation has been initiated, burns to completion before a new molecule is attacked. This can be directly demonstrated by adding intermediates of the tricarboxylic acid cycle to respiring tissues. As already discussed (*see* Table VI) the result of the addition is a suppression of the oxidation of the endogenous substrates, such as glucose or fat.

Whilst this inhibition by intermediates is the rule, it does not apply to the ketotic state where the presence of acetyl coenzyme A or ketone bodies does not suppress the attack of new substrate molecules. The ketotic disorder might thus be looked upon as a failure of acetyl coenzyme A or of ketone bodies to suppress the breakdown of new substrate molecules which yield more acetyl coenzyme A. The reasons for such a failure are still a matter of speculation. There are many factors on which the rate of degradation of a particular foodstuff depends—the activity of the enzymes, the availability of coenzymes and the presence of other foodstuffs. The fact that ketosis can be caused by extracts of the anterior pituitary suggests that pituitary hormones also play a role in co-ordinating acetyl coenzyme A utilization and production. The ketogenic activity of the anterior pituitary appears to be inseparable from its fat-utilizing ("adipokinetic") activity. This would support the assumption that the anterior pituitary plays a part in the control of the rate at which fatty acids are oxidized to acetyl coenzyme A.

How such a control is exerted is unknown. It is likely that the hormone regulates the activity of a key enzyme. Several cases are known where the activity of enzyme is under hormonal control. An example is adrenaline which promotes the conversion of inactive phosphorylase to the active enzyme and thereby accelerates the conversion of glycogen to hexose phosphates (Sutherland and Cori, 1951; Sutherland and Wosilait, 1956; Rall *et al.*, 1957).

Prevention of Ketosis by Dietary Measures

Even without full knowledge of the reasons of ketosis and of the factors controlling the formation of acetyl coenzyme A, ketosis can to some extent be controlled experimentally and therapeutically by dietary measures, i.e. by the administration of antiketogenic instead of ketogenic food. Whether a food is ketogenic or antiketogenic has long been established empirically for the main foods (*see* Magnus-Levy, 1925). The knowledge of intermediary metabolism makes it now possible to predict the ketogenic and antiketogenic properties of food constituents on the following basis.

The energy supply from all foodstuffs comprises two major stages (Scheme 3). The first consists of the reactions leading from the foodstuffs to acetyl coenzymes A or to other intermediates of the tricarboxylic acid cycle. The second is represented by this cycle itself. On ordinary diets, about two-thirds of the energy is set free by the tricarboxylic acid cycle and one-

SCHEME 3.—ENERGY-YIELDING REACTIONS LEADING TO THE TRICARBOXYLIC ACID CYCLE

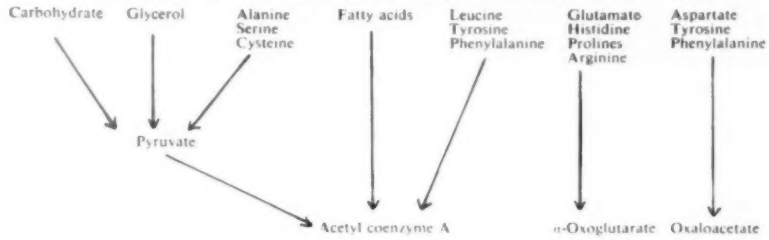


TABLE IX.—RELATIVE AMOUNTS OF ENERGY OBTAINED FROM VARIOUS SUBSTRATES (1) BY OXIDATION OF ACETATE (I.E. TRICARBOXYLIC ACID CYCLE) (2) BY STEPS LEADING TO ACETATE

(The amounts of energy are expressed by amounts of O_2 required and of ATP formed. ATP formation is calculated on the assumption that all oxidative steps yield 3 ATP per one oxygen atom except the reactions α-ketoglutarate → succinate (4 ATP) and $-H_2C-CH_2- \rightarrow -HC=CH-$ (2 ATP). The latter type of reaction occurs in the oxidation of succinate and of fatty acids)

Substrate	Mole O_2 required for: Steps leading to tricarboxylic acid cycle	Mole O_2 required for: Tricarboxylic acid cycle	ATP formed: Steps leading to tricarboxylic acid cycle	ATP formed: Tricarboxylic acid cycle	% of ATP formed through tricarboxylic acid cycle
Carbohydrate (per triose equivalent)	1	2	7*	12	63
Fatty acids (long chains, per each C_2 fraction)	1	2	5	12	71
Fatty acids (C_4-residue or butyrate)	1½	4	5	24	83
Glycerol	1½	2	9	12	57
Lactic acid	1	2	6	12	67
Propionic acid	1½	2	6‡	12	67
Succinic acid	1½	2	8	12	60
Citric acid	2½	2	15	12	44
Glutamic acid	2½	2	15	12	44
Propanol	2½	2	15	12	44
1, 2-Propylene glycol	2	2	12	12	50
Acetic acid	0	2	−2†	12	100
Leucine	1½	6	8	36	82
Tyrosine	3½	6	9§	36	80
Phenylalanine	4	6	12§	36	75

*The ATP formed from carbohydrate includes that formed anaerobically. This amounts to one ATP per triose equivalent when glucose is the starting material.

†Acetic acid requires the expenditure of two pyrophosphate bonds before it can enter the tricarboxylic acid cycle, and yield energy, the reactions by which acetate is activated being:

$$\text{acetate} + \text{ATP} + \text{CoA} \rightarrow \text{acetyl CoA} + \text{AMP} + \text{PP}$$

As far as is known the pyrophosphate is subsequently hydrolysed, and the AMP is phosphorylated by a second molecule of ATP to form 2 ADP:

$$\text{AMP} + \text{ATP} \rightarrow 2\ \text{ADP}$$

The balance of the reaction leading to the entry of acetate into the cycle is therefore

$$\text{acetate} + 2\ \text{ATP} + \text{CoA} \rightarrow \text{acetyl CoA} + 2\ \text{ADP} + 2\ \text{phosphate}$$

‡Like acetate, propionate requires the expenditure of two pyrophosphate bonds, to be converted into its reactive form, i.e. propionyl-CoA. Propionyl CoA is converted to succinyl CoA before it can yield energy and a further molecule of ATP is used for this conversion:

$$\text{propionyl CoA} + CO_2 + \text{ATP} \rightarrow \text{methyl malonyl CoA} + \text{ADP} + \text{P}$$

$$\text{methyl malonyl CoA} \rightleftharpoons \text{succinyl CoA}$$

It is likely that the energy-rich bond of succinyl CoA can be utilized for the generation of ATP through the reactions:

$$\text{succinyl CoA} + \text{GDP} + \text{P} \rightleftharpoons \text{coenzyme A} + \text{GTP} + \text{succinate}$$

$$\text{GTP} + \text{ADP} \rightleftharpoons \text{GDP} + \text{ATP}$$

which are intermediary stages in the oxidation of α-ketoglutarate and are taken to occur in all cells which perform the tricarboxylic acid cycle. It is also known that succinyl-CoA can be used for "activating" acetoacetate through the reaction:

$$\text{succinyl CoA} + \text{acetoacetate} \rightleftharpoons \text{succinate} + \text{acetoacetoyl CoA}$$

and it can thus save ATP required for the "activation" of acetoacetate. Thus, allowing for the net effect of these reactions, 2 ATP molecules are required for the "activation" of propionate.

§Several steps of the oxidation of tyrosine (p-hydroxyphenyl pyruvate → maleyl-acetoacetate, equivalent to 2 O_2) are probably not utilized for the synthesis of ATP (*see* text).

third by the reactions leading to it. A diet can be so modified that the proportion of the total energy supplied derived from the cycle, i.e. from the utilization of acetyl coenzyme A, varies. If ketosis is due to an excess of acetyl coenzyme A, irrespective of whether the excess arises from under-utilization or over-production, it should be relieved by a diet in which less of the energy supply depends on the utilization of acetate and more on the reactions leading to the formation of acetate (it being understood that the total oxygen consumption stays at a given level).

Table IX lists the distribution of the energy-supplying stages between these two phases of metabolism. The list does not aim at completeness but includes substances which may be of therapeutic interest, especially with reference to bovine ketosis. The relative contributions to the energy supply are expressed by two different standards, viz. the amounts of O_2 required and of ATP formed. In calculating the formation of ATP, the assumption has been made that all oxidative steps yield 3 ATP molecules per oxygen atom except the reaction α-oxoglutarate ⟶ succinate which yields 4 ATP and the reaction $-CH_2.CH_2-$ ⟶ $-CH:CH-$ which yields 2 ATP. The latter reaction occurs in the dehydrogenation of succinic and of fatty acids, including propionic acid and the fatty acid derived from leucine, i.e. isovaleric acid. There are uncertainties in the calculation of the ATP yield from tyrosine and phenylalanine because the degradation of these two amino acids includes oxidative steps which probably cannot be coupled with phosphorylation. They are the steps between hydroxy-phenylpyruvate, via homogentisic acid, to maleyl-acetoacetate (Hager *et al.*, 1957; Schepartz, 1953; Knox and Edwards, 1955; Dalgliesh, 1955). The enzyme systems concerned with these stages do not seem to contain pyridine nucleotides, flavoproteins and iron-porphyrins and as a rule only oxidations which involve these catalysts can be coupled to phosphorylation.

The two standards used for measuring the energy supply—O_2 consumption and ATP formation—give in general parallel values, but there are some differences, and the ATP values are of more immediate interest because they are a measure of the *utilizable* energy.

There are three substances in the list which release more than 80% of the energy through the tricarboxylic acid cycle. They are acetate (100%), the C_4-fatty acid (83%), and leucine (82%). These substances are known to be the main ketogenic materials of a normal diet.

Antiketogenic are those substances which relieve the pressure on the tricarboxylic acid cycle by providing energy through reactions outside the cycle. The more energy that can be obtained from reactions other than those of the cycle, the greater this antiketogenic effect can be expected to be. This is in fact the case. According to Table IX, the most effective antiketogenic substances are expected to be propanol, citrate and glutamate. These substances yield more ATP by reactions outside the cycle than is yielded by the cycle itself. The next best substance is 1,2-propylene glycol, followed by glycerol, succinate, propionate, glucose and lactate.

A precise quantitative measurement of the antiketogenic activity in the intact animal is difficult if not impossible, but qualitatively the experience gained from experiments on the ketosis of starvation, of pancreas diabetes and of cows suffering from bovine ketosis is as expected. The results of earlier experiments on the antiketogenic effects of various substances have been summarized by Magnus-Levy (1925). The antiketogenic effect of glucose has long been known. Those of lactate, glycerol, citrate, glutamate and propionate have been observed on humans and on dogs by Baer and Blum (1907), Satta (1906), and Borchardt and Lange (1907). More recently their antiketogenic effects, as well as those of 1,2-propylene glycol, have also been noted in cases of bovine ketosis (Schultz and Smith, 1951; Schultz, 1952, 1954; Johnson, 1951, 1954; Mills, 1954; Maplesden, 1954). In testing the antiketogenic activity, complications may arise when the substance under test is acidic and administered as an alkali salt. Neutral substances have probably the advantage of greater palatability and of rendering unnecessary an intake of a major quantity of alkali.

There is thus sufficient information to supplement a diet so as to make it less ketogenic.

Hormonal Therapy

Since, however, the type of energy-supplying reaction—whether energy is derived from carbohydrate, fat or protein—is not solely controlled by the diet but also by hormones, methods of treatment may be based on either dietary changes or hormonal supplements. An example of the effectiveness of a hormonal supplement is the insulin therapy of diabetes, and insulin is certainly also the most effective remedy for those types of ketosis where carbohydrate cannot be utilized because of lack of insulin, i.e. the common forms of diabetic ketosis. It is of course of no avail when it is not a limiting factor in carbohydrate utilization, as is the case in bovine ketosis. Numerous reports have appeared in recent years on the successful treatment of this type of ketosis

with cortisone, hydrocortisone and related substances (Shaw, 1955, 1956; Paterson, 1957; Gessert *et al.*, 1955; Shaw *et al.*, 1955; Link *et al.*, 1957; Vigue, 1955). The glucocorticoids are antiketogenic because they inhibit the degradation of fat and favour the utilization of carbohydrate. The mechanism of action of these hormones is not yet known in detail, but its study is a field now ready for further experimental work. The immediate problem is to pin-point the enzymes of fat and/or carbohydrate metabolism on which these hormones act.

Whilst, thanks to insulin, the problem of treating diabetic ketosis is now well in hand, this cannot be said with equal confidence of bovine ketosis in which, however, the difficulty is in practical management rather than ignorance of basic principles. A pattern for the treatment of ketosis is provided by the experience of diabetes mellitus in man. Diabetes, like bovine ketosis, is primarily an upset of endocrine balance and in this type of condition the two therapeutic approaches, dietary and hormonal, aim at restoring to normality a dis-equilibrium: to replace the deficient hormone by supplements and to modify the diet in order to assist the body's diminished capacity for maintaining the metabolic balance. In some cases, depending on the type and severity of the disease, one method of treatment, either dietary or hormonal, may be adequate. In other cases, a combined dietary and hormonal treatment is called for.

Conclusion

The development of biochemical knowledge has substantially deepened our understanding of ketosis but the final answer to the question of why ketone bodies accumulate under certain conditions still cannot be given. The newer knowledge allows us to formulate the problem more precisely: in ketosis, acetyl coenzyme A or acetoacetate fail to prevent the oxidation of substrates which provide further acetyl coenzyme A. This is in contrast to the general rule that intermediates do not accumulate because their presence suppresses the degradation of the material from which they arise. Full understanding of the ketosis problem will have to await more information on how the degradation of foodstuffs is controlled, but, on the practical side, enough information is available to treat ketosis effectively in man and in farm animals.

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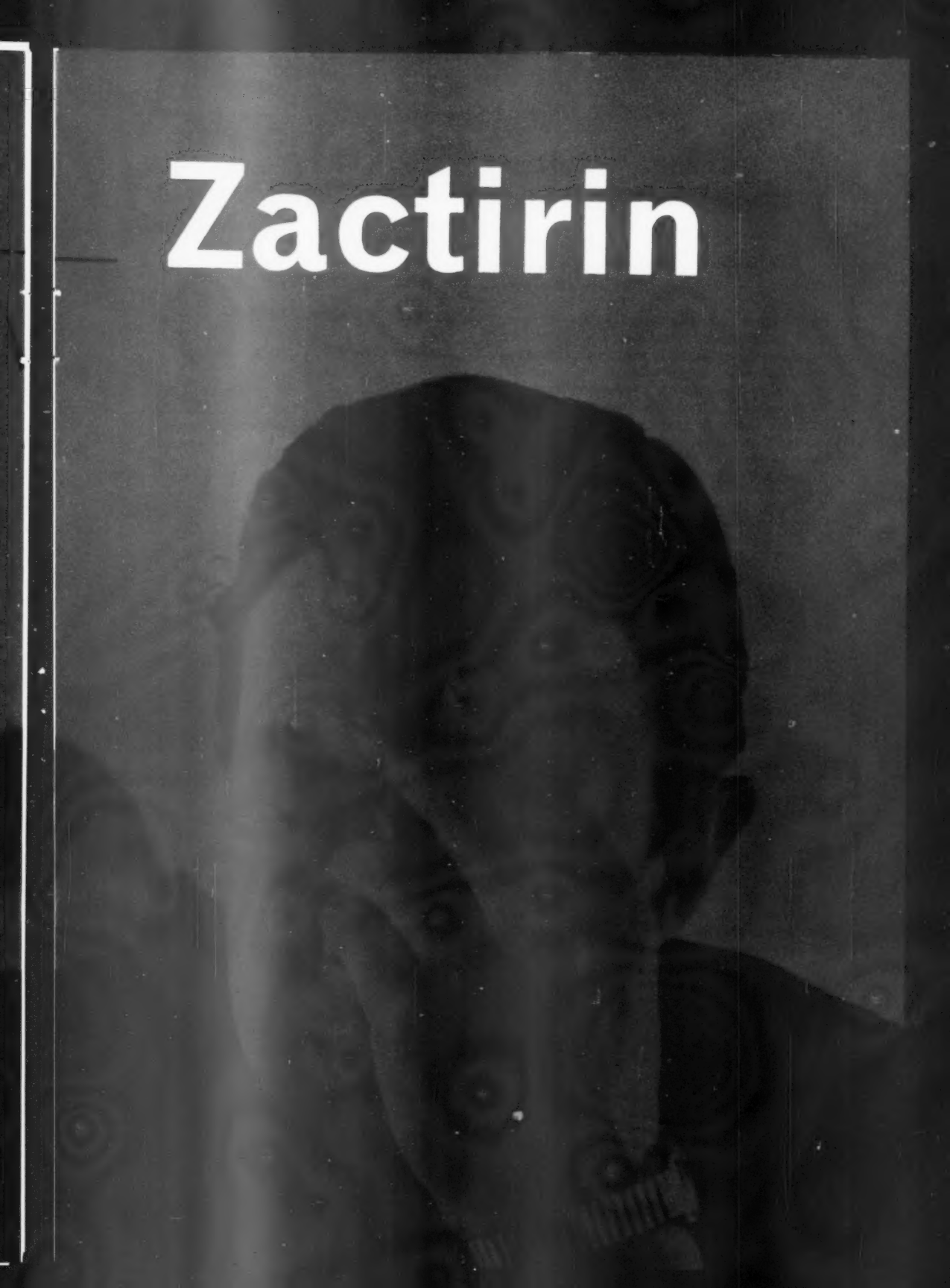

Section of Endocrinology

President—Professor F. T. G. Prunty, M.D., F.R.C.P.

Meeting
October 28, 1959

DISCUSSION ON THE ASSESSMENT OF ENDOCRINE FUNCTION AFTER HYPOPHYSECTOMY OR PITUITARY DESTRUCTION

Professor Russell Fraser and **Dr. G. F. Joplin** (London):

Assessment of Pituitary Function after Pituitary Ablation

In 1941 Fraser and Smith proposed certain tests which could be used to confirm the rather vague syndrome described by Simmonds in 1914. Sheehan and Summers (1949) have found that 85–95% of anterior pituitary tissue is usually destroyed before Simmonds' syndrome develops; lesser degrees of pituitary destruction neither produce the syndrome nor give rise to abnormal tests. Thus when abnormal tests are obtained after attempted ablation of the pituitary, there is good reason to believe that the function of more than 95% of the hypophyseal tissue has been destroyed.

However, the results of these tests may be influenced not only by the pituitary ablation but also by widespread malignant disease. Provided those least influenced by cachexia alone are chosen, indirect tests of thyroid and adrenal function are satisfactory for assessing pituitary destruction, although a special series of tests is necessary for the few patients who have been adrenalectomized before they have been hypophysectomized. In studying severely ill patients it is preferable to use tests which can easily be repeated provided they are sufficiently sensitive and specific.

For these reasons the tests used have mainly been a radioiodine test for thyroid function and the water diuresis test (W.D.T.) for adrenal function together with an electrocardiogram. When these give an abnormal result, the estimation of urinary gonadotrophin excretion has often been performed in addition. No reliance has been placed on urinary steroid excretion because this is often seriously reduced in malignant and other cachectic states without there being any pituitary involvement. We have, however, noted whether patients developed clinical evidence of acute cortisol deficiency after cortisone is withdrawn on the tenth post-operative day.

The development of clinical dependence on exogenously administered cortisone indicates a severe degree of hypopituitarism, and we have used this as a clinical criterion against which to measure the adequacy of pituitary function tests in the presence of carcinomatosis. We have been concerned in assessing the adequacy of pituitary ablation after needle implantation of radioactive yttrium (^{90}Y) but the tests should be equally applicable after surgical hypophysectomy although any return of pituitary function is less likely after treatment with ^{90}Y because of irradiation to any pituitary remnants.

The tests were first done ten to fourteen days after the implant and thereafter at intervals of three to six months to check the persistence of any abnormalities. During the first week after the operation the patients received 50 mg cortisone daily which was gradually reduced and stopped over the seventh to tenth post-operative days. The first water diuresis test was done on the twelfth day—thirty-six hours after the last dose of cortisone. During the next week a radioiodine test was done and the patient watched carefully for clinical evidence of cortisol deficiency. If this developed the W.D.T. was repeated and then appropriate treatment instituted. If no evidence of cortisol-deficiency developed within two weeks of stopping cortisone, the tests were usually normal and a decision was taken as to whether a further implant should be done.

Results

The results of these tests have been assessed in 35 patients who have been followed for three to forty-eight months following implantation. Fig. 1 shows that the results of the first radioiodine tests carried out after implantation gave a good indication of subsequent pituitary function. The patients are grouped according to the mean result of the several post-implantation radioiodine tests. It is evident that the initial separation of the groups is maintained during later months.

The patients can be divided into two clinical groups: the "cortisone-dependent" cases who developed evidence of acute cortisol-deficiency when cortisone was withdrawn in the post-operative period and therefore had clinical

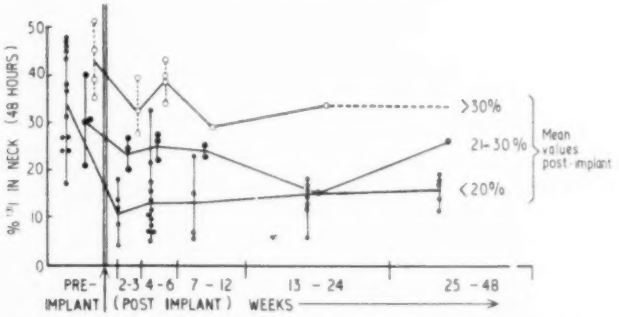

FIG. 1.—Serial radioiodine tests after pituitary implantation with ^{90}Y. (35 cases, grouped by mean post-implant values.)

hypopituitarism, and those who did not develop the withdrawal syndrome and who presumably had insufficient pituitary destruction.

Water diuresis test.—This is simple, cheap and needs only a short period of accurate urine collection. Only a small water load of 1 litre has been used so as to avoid nausea, and it must be suitably flavoured with lemon or even tea. Because the result may be abnormal in heart failure or renal disease, it is important to ascertain the pre-operative value. If any difficulty in interpretation arises, the test should be repeated after full substitution with cortisone. The contrasting results in patients with and without cortisone dependency is shown in Fig. 2. Corti-

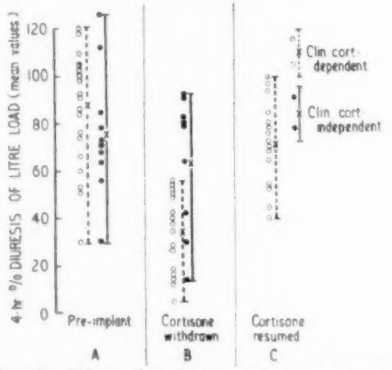

FIG. 2.—Water diuresis test results: A, pre-implant; B, not on cortisone (between twelfth and nineteenth day post-implant); C, after full clinical restoration with resumed corticosteroid dosage. The patients are grouped according to development of cortisol-deficiency syndrome after cortisone withdrawal. Each plot is the mean of all test results for the patient while in the phase.

sone administration for ten days post-operatively does not seem to have reduced the reliability of this test of adrenal function: the incompletely hypophysectomized patients showed no significant adrenal suppression, and the results in the cortisone-dependent group were in general agreement with other assessments of pituitary function. During withdrawal of cortisone repeated tests were made until clinical cortisone-dependency was clearly established—the last test usually giving the most abnormal result. The mean four-hour diuresis in the adequately hypophysectomized patients not receiving cortisone was usually less than 50% or 500 ml, the volume being on average at least 380 ml less than the value obtained either pre-operatively or after full substitution with cortisone (Fig. 2). In very ill patients or those whose endocrine status is uncertain, it is important to establish that a reduced water diuresis can be returned to normal with cortisone treatment.

In several patients serial tests during the initial cortisone withdrawal period and during subsequent restoration with corticosteroids throw some interesting and practical light on the speed with which this renal tubular abnormality develops and then recovers with heavy substitution dosage (Figs. 3A and 3B). The restoration dosage was not standardized at first but did approximate our current regime which is 20 mg prednisone immediately, followed by 5 mg hourly for six hours and thereafter 5 mg four-hourly until there is full clinical recovery and restoration of a normal diuresis, when the dosage is changed to the standard maintenance of 12·5 mg cortisone eight-hourly. Often there is a clearly abnormal result on the second day of cortisone withdrawal (Fig. 3A) and the response may steadily decrease to a maximum abnormality usually attained by the seventh day. Only one patient had an abnormally small diuresis on the second day but later a normal result without cortisone. Correspondingly the restoration of a normal diuresis tends to

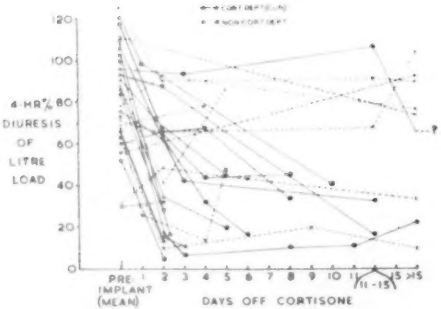

FIG. 3A.—Serial water diuresis tests during the first post-implant cortisone withdrawal period.

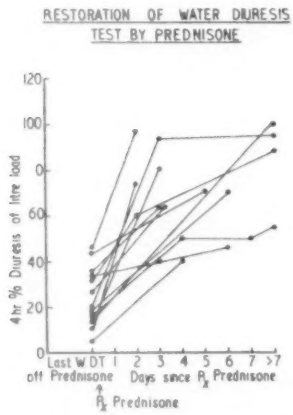

FIG. 3B.—Serial water diuresis tests during full prednisone restoration.

be gradual over a period of about seven days even with heavy prednisone dosage. This slow return to normal is analagous to that of the hypothyroid abnormalities on administration of thyroxine (Ibbertson *et al.*, 1959): probably both require some gradual restoration of tissue enzymes before full cellular responsiveness to the hormone is attained.

Our conclusions regarding the water diuresis test are therefore that (1) the test should be done on the second day of cortisone withdrawal; (2) it should be repeated on the day the cortisol-deficiency syndrome develops or at the latest on the seventh day (if insufficiently abnormal, incomplete hypophysectomy is implied); and (3) when a test after corticosteroid restoration is needed it should be done on the seventh day of full prednisone treatment as outlined above.

Radioiodine.—This test, which can be carried out with or without cortisone maintenance, is usually done after the water diuresis test. Though it is perhaps the best index of hypophysectomy, by itself it is not sufficient because management of the patient demands knowledge about the patient's clinical dependence on cortisone. The most satisfactory radioiodine test is the forty-eight-hour neck uptake. Subdivided urinary collections may also be made but collections are not always reliable in these patients. Because the normal limits of the 48-hour protein-bound ^{131}I test extend to very low values, this is not reliable for demonstrating hypofunction. Although in many patients with definite but moderate Simmonds' disease the forty-eight-hour neck uptake may be normal (Fraser *et al.*, 1953), this is of no disadvantage in cancer patients in whom a severe degree of hypopituitarism is required and in whom therefore there should be a significant lowering of the neck uptake. 16 of the 19 patients who were clinically cortisone-dependent had a forty-eight-hour radioiodine uptake of less than 25% whereas in 5 of the 9 cortisone-independent patients it was normal (Fig. 4).

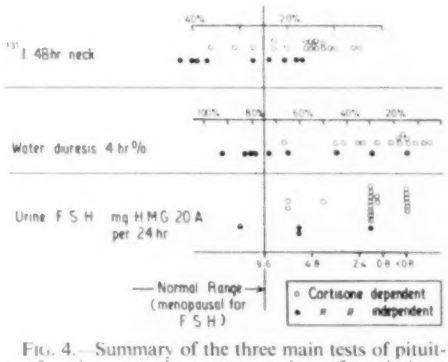

FIG. 4.—Summary of the three main tests of pituitary function at twelve to twenty days after pituitary implant, contrasting patients with and without cortisone-dependency.

Electrocardiogram.—This is an important supplementary test, especially in the initial post-operative cortisone withdrawal phase. When the cortisone-withdrawal syndrome is observed, an ECG is taken before treatment with prednisone is started. Restoration of any abnormalities, particularly T-wave changes, can be re-examined on the seventh day after full corticosteroid restitution. It is important to remember that later a deficiency of thyroxine will produce its own ECG abnormalities. However, after full thyrox-

ine replacement the ECG may again be used to detect cortisone-dependence. Within two weeks of pituitary destruction there is still enough thyroid hormone in the tissues to enable the ECG to reflect the tissue supply of cortisol.

The results obtained with the two chief tests—water diuresis and radioiodine uptake—during the post-implantation phase are shown for the cortisone-dependent and cortisone-independent patients in Fig. 4. Also shown are the results of F.S.H. estimations in some of the patients. 3 of the clinically hypopituitary patients did not have an abnormal radioiodine test and may, therefore, have had a sub-optimal hypophysectomy. In the cortisone-independent group the radioiodine test was normal or near-normal. The results of the water diuresis test in the cortisone-dependent patients are those obtained in the last test done while not on cortisone and just before corticosteroid replacement. All are abnormal. The single near-normal value of 66% was in an exceptional patient who did not show cortisone dependency until three weeks later. Two of the low values could not be restored to normal by cortisone and probably reflect a cardiovascular or renal abnormality. In the cortisone-independent group, the diuresis values are the mean of several tests done after cortisone withdrawal. No constant trend was observed. The lowest value of 14% could be partially restored by cortisone; the response to cortisone was not tested in the patient with the next lowest value of 30%, while the third lowest (42%) was an improvement on values obtained before implantation.

The F.S.H. values confirmed pituitary destruction by being abnormally low in all but 3 of the cortisone-dependent patients. More results are needed in the other group to decide whether this test may not prove too sensitive. A comparison of these three tests suggests that radioiodine uptake may be the more stringent criterion, since it was normal in a few cases with adrenal insufficiency and low gonadotrophins.

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Mr. A. P. M. Forrest, Mr. A. W. Sim and Dr. Helen J. Stewart (Glasgow):

Pituitary Function Tests After Radioactive Implantation of the Pituitary

The extent of pituitary destruction following radioactive implants can be assessed quantitatively by histological examination of the contents of the sella turcica after death. In this way the effect of implanting either radon seeds, or rods or screws of yttrium-90 into the pituitary fossa has been estimated in 62 women with advanced malignancy (Dr. A. T. Sandison). The methods of implantation and examination of the pituitary have been described elsewhere (Forrest *et al.*, 1959). The results reveal that only by ^{90}Y screw-implantation can consistently complete or near-complete destruction be assured, destruction being defined as complete loss of cell outlines and nuclei; recognizable cells with nuclei are regarded as viable, although they may have received sufficient radiation to impair their function.

Various biochemical tests have been used to measure the extent of pituitary destruction during life and we have correlated these with the extent of the destruction found after death.

Pituitary Hormones

Gonadotrophins.—Using the method of Loraine and Brown (1954), no gonadotrophin was found in the urine of 4 patients treated by implantation of the pituitary with radon seeds, despite incomplete anatomical destruction of the gland in 3 of them. In an acromegalic with breast cancer treated by ^{90}Y implantation, urinary gonadotrophins could not be detected although suppression of 17-ketosteroid secretion by prednisolone clearly indicated persistent pituitary function. Thus absence of gonadotrophic activity in the urine, estimated by the methods at present available, is not evidence of complete anatomical destruction of the pituitary gland.

Adrenal and Ovarian Hormones

Estimations of neutral 17-ketosteroids, their 11-oxy and 11-deoxy fractions and œstrogens in the urine, and 17-hydroxycorticosteroids in peripheral blood, were done in patients with breast cancer after radioactive implantation of the pituitary, both while receiving maintenance cortisone therapy and when this was temporarily discontinued.

Total neutral 17-ketosteroids were estimated by the modified Callow-Zimmerman method (Medical Research Council, 1951) and their 11-oxy and 11-deoxy fractions by the methods previously described by Hobkirk (1958). Urinary

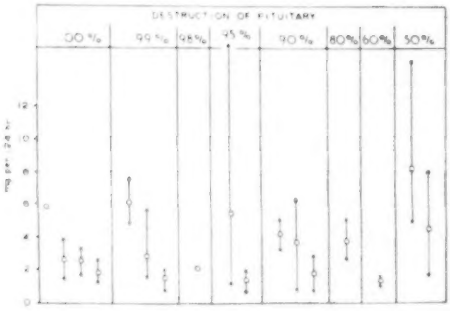

FIG. 1.—Total neutral 17-ketosteroids in the urine of 17 patients with breast cancer after implantation of the pituitary with ^{90}Y. The means and ranges of all estimations carried out within six months of implantation while patients were receiving 50 mg cortisone a day are shown.

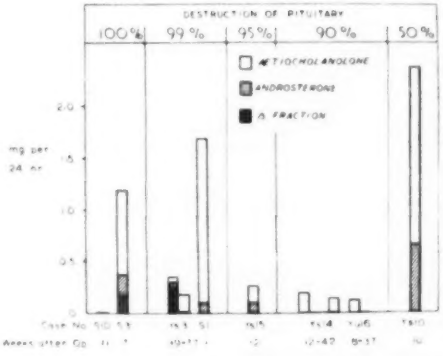

FIG. 2.—Urinary 11-deoxy 17-ketosteroids in 8 patients with breast cancer after implantation of the pituitary with ^{90}Y.

œstrogens (œstriol, œstrone and œstradiol-17β) were estimated by Brown's method (Brown, 1955; Brown *et al.*, 1957) and plasma 17-hydroxycorticosteroids by a modification of the Porter-Silber technique (Porter and Silber, 1950). As the penetrating gamma rays emitted by radon are more likely to cause functional damage to histologically normal cells which surround the zone of complete necrosis, only estimations carried out in patients following ^{90}Y implants, which emit only beta particles, have been considered.

Estimations during cortisone substitution therapy.—Repeated estimations of the twenty-four-hour excretion of total neutral 17-ketosteroids were made in 17 patients after ^{90}Y implantation of the pituitary and while on maintenance cortisone therapy (50 mg per day). The mean value for each patient was not related to the extent of pituitary destruction as determined after death (Fig. 1). Estimations of 11-oxy 17-ketosteroids in seventy-two-hour pools of urine were similarly without significance. These steroids (11-hydroxyætiocholanolone, 11-hydroxyandrosterone, 11-ketoætiocholanolone, 11-ketoandrosterone) are mainly metabolites of glucocorticoids and thus of the cortisone administered to the patient.

The 11-deoxy 17-ketosteroids (ætiocholanolone, androsterone and dehydroepiandrosterone) are metabolites of the androgens (mainly Δ^4 androstene 3 : 17 dione) of adrenocortical, and in the case of ætiocholanolone partially of ovarian

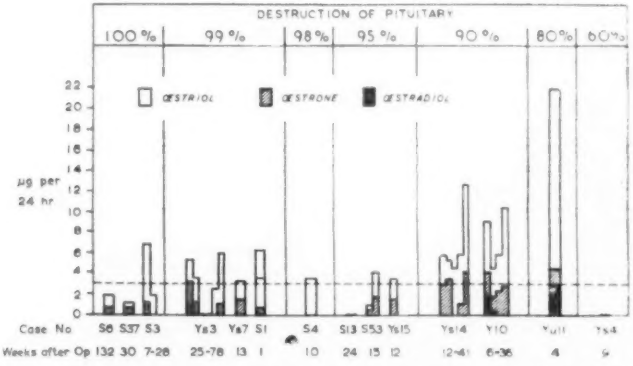

FIG. 3.—Urinary œstrogens in 14 patients with breast cancer after implantation of the pituitary with ^{90}Y. (In Figs. 2 and 3 estimations were made on seventy-two-hour collections of urine while cortisone 50 mg per day was being taken.)

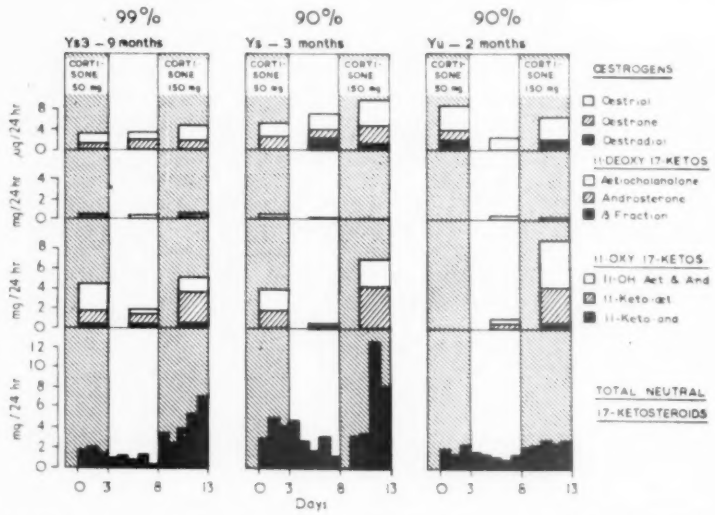

FIG. 4.—Urinary steroids during cortisone withdrawal in 3 patients with breast cancer treated by implantation of the pituitary with ^{90}Y and subsequently shown to have 99%, 90%, and 90% of the pituitary gland destroyed.

origin (Birke *et al.*, 1958). They are not significantly derived from endogenous or exogenous cortisol. These ketosteroid fractions can rarely be detected in the urine of patients with breast cancer after total adrenalectomy and oophorectomy whether cortisone is being taken or not. After pituitary implantation with ^{90}Y the amounts detected in the urine were generally low provided that 90 to 100% of the gland was destroyed (Fig. 2). Of 2 patients with complete destruction of the gland one still excreted significant amounts of all three steroids seven weeks after implantation; in the urine of the other none was detected.

Recoverable amounts of œstriol, œstrone and œstradiol-17β, estimated chemically, may still be present in the urine of women with breast cancer after adrenalectomy and oophorectomy. After pituitary implantation the amounts present were roughly inversely proportional to the extent of destruction of the gland. However, in 3 patients with 99% destruction and in 1 with complete destruction significant quantities were still detected in the urine while in a patient with only 60% destruction none was recovered (Fig. 3).

Estimations during cortisone withdrawal.—In our experience adrenalectomized women can tolerate cortisone withdrawal for thirty-six hours to five days. During this period those urinary steroids which are metabolites of cortisol progressively fall to zero or near-zero levels (11-oxy 17-ketosteroids and total 17-ketosteroids) while 17-hydroxycorticosteroids disappear from the peripheral blood. The 11-deoxy 17-ketosteroids are absent from the urine whether cortisone is taken or not and the excretion of œstrogens and pregnanediol are unaffected by the absence of cortisone (Hobkirk *et al.*, 1959).

After surgical hypophysectomy (Lipsett *et al.*, 1957) or radioactive implantation of the pituitary, patients remain well without cortisone therapy for longer periods of time and in most no ill-effects occur during a five-day period of cortisone withdrawal. Estimations of urinary steroids have been carried out in several patients after ^{90}Y implantation before and during a five-day period of cortisone lack and during the subsequent five days when cortisone was restarted in a larger dose (150 mg/day). The patterns of urinary steroids for 3 such patients in whom anatomical destruction of the pituitary was subsequently shown to be 99%, 90% and 90% respectively are shown in Fig. 4. In all 3 patients the total 17-ketosteroids, 11-oxy and 11-deoxy fractions and œstrogens behaved similarly notwithstanding the difference in the extent of damage to the gland.

In 2 patients daily estimations of plasma 17-hydroxycorticosteroids were carried out during cortisone withdrawal; in both patients they fell to undetectable levels despite incomplete destruction of the gland in one. In a patient with a

stricture of the bile duct who had been treated by cortisone 50 mg per day for four months, abrupt withdrawal of the cortisone also resulted in a fall of 17-hydroxycorticosteroids in the plasma to irrecoverable levels. The results in hypophysectomized patients maintained on cortisone are therefore not a reliable test for residual pituitary function.

Prednisolone suppression test.—In 2 women with breast cancer treated only by mastectomy the excretion of neutral 17-ketosteroids was reduced by the administration of prednisolone 50 mg per day for six days compared with that on a similar dose of cortisone. 3 patients treated by pituitary ^{90}Y implantation failed to show this response; the histological assessment of gland destruction was 90% in 2 and 99% in the third.

Conclusions on adrenal function tests.—While the results of these tests suggest that adrenocortical function is markedly depressed following effective implantation of the pituitary with ^{90}Y, it is difficult to decide to what extent these hormone assays can differentiate between the completely destroyed pituitary and that in which small groups of histologically normal cells remain. In patients treated by pituitary irradiation this difficulty is increased by the impossibility of knowing whether these residual cells are capable of function. The effect of replacement cortisone therapy in depressing adrenocortical function may also lead to difficulty in evaluating the tests and clearly merits further study.

It has been shown in man that conservation of salt, an aldosterone effect, is unaffected by hypophysectomy (Maclean *et al.*, 1957) which may account for the greater tolerance to the absence of cortisone shown by hypophysectomized as compared to adrenalectomized patients. Our finding of significant excretion of 11-deoxy 17-ketosteroids despite complete destruction of the pituitary suggests that the unstimulated adrenal may also secrete androgenic steroids.

From studies carried out in collaboration with Dr. J. Grant, Department of Biochemistry, University of Edinburgh, and Dr. R. Short, School of Veterinary Medicine, Cambridge, it appears likely that cortisol synthesis also can take place in the human adrenal gland after complete pituitary destruction. In a patient with breast cancer, treated by ^{90}Y rod implant two and a half years and ^{90}Y screw implant four months previously and later found to have complete destruction of the pituitary, significant amounts of cortisol (14·8 μg/100 ml plasma) were found in a sample of adrenal venous blood collected during adrenalectomy. No significant cortisol was present in a sample of peripheral blood taken simultaneously (<5 mg/100 ml plasma). The steroid-hydroxylating capacity of the removed adrenal, which weighed only 2 g, was investigated *in vitro;* using 11-deoxycorticosterone as substrate it was found that a homogenate of the gland was capable of 11β-hydroxylation and produced corticosterone to a limited but significant extent (29 μg/mg N/h).

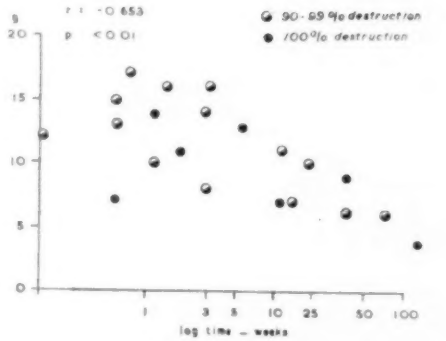

FIG. 5.—Post-mortem adrenal weights in 24 women with breast cancer treated by radioactive implantation of the pituitary.

The excretion of adrenal hormones and their metabolites may also be influenced by the time since implantation of the pituitary, for the adrenal weight at post-mortem has a highly significant negative correlation with the logarithm of the

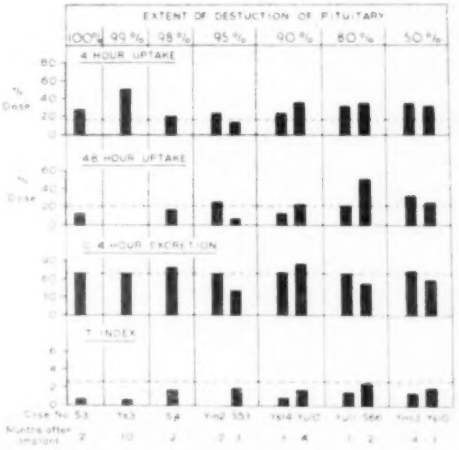

FIG. 6.—Results of ^{131}I tests of thyroid function in patients with breast cancer after implantation of the pituitary with ^{90}Y. The extent of destruction of the gland is also shown.

time between pituitary implantation and death (Fig. 5). Thus atrophy of the adrenals after pituitary destruction is a slow process. Adrenal weights in patients with 90 to 99% destruction of the pituitary were similar to those in patients in whom it was complete.

Thyroid Function

After ^{90}Y implantation of the pituitary clinical signs of myxœdema appear in three to six months and tests of thyroid function using ^{131}I confirm low activity of the gland (Fig. 6) (Dr. James Crooks). Although the four-hour uptake may remain normal even when destruction of the gland is extensive, the forty-eight-hour uptakes and T index of urinary excretion are markedly depressed and most of the radioiodine is excreted within forty-eight hours. The T index in particular is related to the extent of destruction although it is still abnormally low when only 50% of the gland is necrosed. Post-mortem thyroid weights were very variable and not related to the time since implantation of the pituitary.

General Conclusions

The results indicate that following implantation of the pituitary with ^{90}Y using the fixed source or screw technique 95 to 100% destruction of the gland can be consistently achieved. While it cannot be clearly defined to what degree function of the adrenal and thyroid glands persists after even a complete hypophysectomy, absent or low 11-deoxy 17-ketosteroids in the urine, a fall in 11-oxy 17-ketosteroids when cortisone is discontinued and a low T index of radioiodine excretion would at least suggest that the function of the gland was severely disturbed.

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Dr. D. N. Baron (London):

Investigation of Anterior Pituitary Function after Surgical Hypophysectomy

The ideal method for studying the completeness of hypophysectomy is to examine the pituitary fossa after death and to correlate retrospectively the autopsy findings with the results of biochemical tests done during life. However, it is extremely difficult to correlate the histological appearances of the anterior pituitary with its physiological activity. Nor is it certain how much remaining tissue—itself difficult to assess—is necessary for normal endocrine activity. We consider that a thin rim of persisting pituitary cells is compatible with functionally complete hypophysectomy. Activation of the vestigial pharyngeal pituitary has been said to occur after hypophysectomy, but this has not been substantiated. In most of our cases the technique used (by Mr. E. J. Radley Smith) has been surgical removal of the gland through a right frontal approach followed by implantation of 15 μc of unscreened radioactive gold seeds under direct vision (Baron *et al.*, 1958).

Tests measure pituitary activity only at the time of testing and remnants of pituitary tissue, inactive in the immediate post-operative period, may become functional later. When tests give equivocal results they are best repeated after a three-month interval when either further atrophy will have occurred or activity returned towards normal. We have found that the best time to assess pituitary function initially is three to four weeks post-operatively (Baron and Gurling, 1960).

Of the anterior lobe hormones only F.S.H. and L.H. can be assayed; the validity of the methods claimed for prolactin has not been established. Urinary gonadotrophin assay has been performed on many of our patients by Dr. Ian Somerville using the mouse uterine assay method following kaolin absorption (Loraine and Brown, 1956). This method is valid only if appreciable levels are present pre-operatively; in 8 of 38 women investigated less than 6 mouse units/twenty-four hours were found pre-operatively. If the pre-operative value is above 24 units, the level three to four weeks after operation falls to undetectable amounts when pituitary function is absent. Persistent excretion above 24 units indicates continued pituitary activity. Although this biological assay is useful as a direct measure of pituitary function we do not consider it as informative as tests of thyroid or adrenal function.

Changes in thyroid function provide the easiest

means of assessing the completeness of hypophysectomy, and ^{131}I studies have been found more informative than the B.M.R. or serum cholesterol level. Clinical myxœdema is apparent in 60% of patients by the fourth postoperative week if thyroid replacement is not begun earlier. The B.M.R. steadily declines after operation, but diagnostic values may not be reached by four weeks: it is the decline and not the absolute value which is important in assessing thyroid deficiency. In only one-third of our patients was a level diagnostic of myxœdema found at the time of testing. Perhaps because the duration of thyroid deficiency was short, the serum cholesterol was normal in half our patients.

We have found the plasma ^{131}I activity forty-eight hours after a dose of 45–60 μc the most useful type of test and the conversion ratio the best single test (Goodwin *et al.*, 1951). In more than 80% of patients who were clinically considered to be completely hypophysectomized these tests gave confirmatory results. A few patients have been found with autonomous functioning thyroid adenomas in the absence of any detectable pituitary function: in such cases diffuse activity is absent (Gurling *et al.*, 1959).

Adrenal activity is estimated by measuring urinary or plasma corticosteroids after cortisone replacement therapy has been withdrawn for seventy-two hours. Although the values decline to very low levels in complete hypophysectomy no clinical symptoms more severe than anorexia and lethargy have been seen, and this cortisone withdrawal test is considered completely safe. The occurrence of more severe symptoms after another week provides additional clinical evidence of absent adrenocortical function. Plasma levels fall more rapidly than urinary excretion, and we have found that they usually give more clear-cut results. Occasionally detectable urinary corticosteroids have been found when all other evidence has suggested complete hypophysectomy. This may correlate with the occasional persistence of plasma conjugated corticosteroids after cortisone withdrawal when free corticosteroids are absent. Free and conjugated corticosteroids were measured independently in plasma samples (15 ml) by the Porter-Silber reaction (Baron *et al.*, 1960). The plasma was always taken at 10 a.m., which is a few hours after the usual diurnal peak, but is convenient and gives reasonably high results. The normal range of plasma corticosteroids was: free 8–20 μg/100 ml; conjugated 5–17 μg/100 ml. The extinction point by our procedure was 3 μg/100 ml. After cortisone withdrawal the free fraction is normal when there is other evidence of continuing pituitary function: in completely hypophysectomized patients the free fraction is below normal, and often absent. The control series was given a similar dose of cortisone (37·5–50 mg daily) for three to four weeks; the same cortisone withdrawal test was done and the free fraction was always normal at seventy-two hours (Table I).

The plasma corticosteroids were studied by chromatography in certain patients. In those who were considered completely hypophysectomized no steroids could be seen in the seventy-two-hour specimen of the cortisone withdrawal test. Unfortunately no incompletely hypophysectomized cases were examined. We consider that our method is sensitive to about 1·5 μg of cortisol/100 ml plasma.

These tests of adrenal function are invalid for the assessment of hypophysectomy if the patient has impaired adrenal function pre-operatively due to metastases, or has been adrenalectomized.

Our experience on the value of sex hormone estimations, which largely measure adrenal function, has been confined to assay of androgen metabolites. Theoretically urinary pregnanediol excretion could be used as a reflection of progesterone secretion by the adrenal cortex or corpora lutea, but I know of no extensive studies after hypophysectomy. Estimation of urinary œstrogens is difficult, and a valid method for low concentrations has only recently been developed. Accordingly some results reporting continued œstrogen secretion after apparent complete hypophysectomy await confirmation.

Urinary 17-oxosteroids represent principally

TABLE I.—RANGE OF FREE AND CONJUGATED PLASMA CORTICOSTEROIDS AFTER CORTISONE WITHDRAWAL TEST

Condition of subjects	Total number of subjects	Number of subjects in each range of plasma corticosteroids at 72 hours—μg/100 ml					
		Zero (<3)		Low (3–8) (3–5)		Normal (>8) (>5)	
		Free	Conj.	Free	Conj.	Free	Conj.
Complete hypophysectomy ..	29	21	18	7	8	1	3
Incomplete hypophysectomy ..	5	0	0	0	2	5	3
Control	5	0	0	0	1	5	4

adrenal androgen secretion but some administered cortisone is excreted as 17-oxosteroids. Total 17-oxosteroid analysis can be valid only in a cortisone withdrawal test. Though zero levels are not found if anterior pituitary function is present, the urinary excretion may decline slowly (as for corticosteroids) and the steroids be present after complete hypophysectomy. Dehydro*epi*androsterone (DHA) is secreted solely by the adrenal cortex under the stimulus of ACTH. The absence of urinary DHA in completely hypophysectomized cases, when on or off cortisone, and its continued presence in incompletely ablated cases, have been shown (Khattab, 1956; Holliday *et al.*, 1958). Unfortunately this method is only available as a difficult research procedure. Similarly estimations of total or differential plasma 17-oxosteroids can only be undertaken in a special unit.

Acknowledgments.—The metabolic studies reported here were performed with the financial assistance of the British Empire Cancer Campaign. I would like to thank Mr. E. J. Radley Smith for his support, and Mrs. Marion Gore, Ph.D., Dr. K. J. Gurling and Mr. H. S. Williams, M.Sc., for their collaboration in this work.

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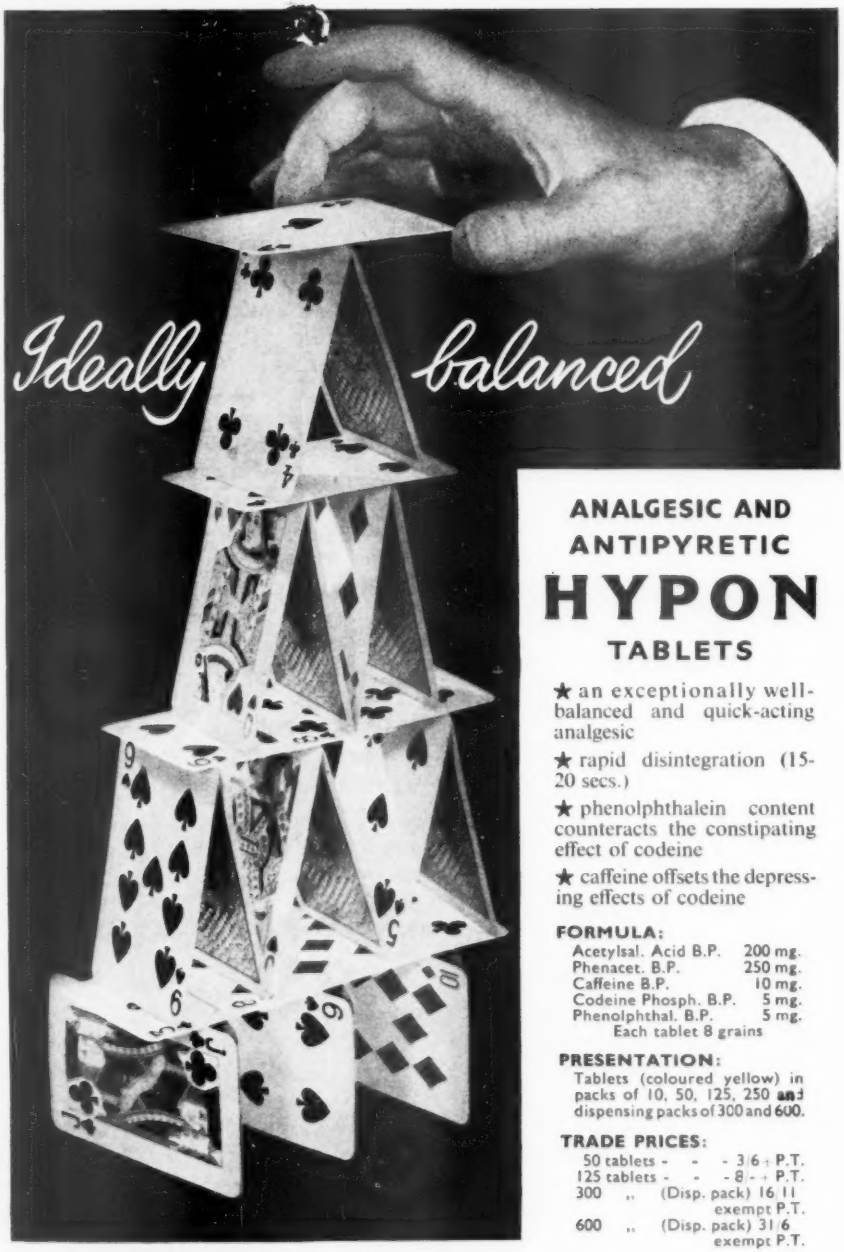

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Proceedings of the Royal Society of Medicine

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United Services Section

President—Air Marshal Sir HAROLD WHITTINGHAM, K.C.B., K.B.E.

Meeting
October 1, 1959

RECENT ADVANCES IN THE APPLIED PHYSIOLOGY OF FLIGHT

SYMPOSIUM BY THE ROYAL AIR FORCE INSTITUTE OF AVIATION MEDICINE

Flight Lieutenant J. D. Nelms, R.A.F.:

Acclimatization to Cold in the Hand [Abstract]

There is convincing evidence that animals acclimatize to continuing cold stress by metabolic response, both in the muscular and visceral systems. General acclimatization to cold in man continues to present a confusing picture and will not be reviewed in this presentation. However, there is good evidence for peripheral circulatory acclimatization in man, and recent work among Arctic Kutchin Indians at Old Crow, Yukon Territory, has added further facts. The technique employed was the measurement by calorimetry of hand heat output when exposed to cold water, the subject being bodily warmed or cooled. The results show significantly higher heat outputs and, by inference, increased blood flow to the hands, in Indians than in control Whites. This result is more marked when body cooling is superimposed on hand cooling. Hand skin temperature measurements show, in response to ice water immersion, that the Indians have a significantly earlier, more emphatic cold vasodilatation reaction, which is in conformity with their observed ability to work in very cold water. The expedition was led by Dr. L. Irving, and the participants were: A. Bolstad, R. Elsner, J. Hildes, K. Lange Andersen, Y. Loyning, J. Nelms, L. Peyton and R. Whaley.

Flight Lieutenant J. Billingham, R.A.F.:

Practical Problems of Protection Against the Heat

Introduction.—Physiological defence mechanisms against the heat enable healthy man to withstand satisfactorily all naturally occurring hot climates. Even in Death Valley, man will be safe provided he has plenty of water to drink. However, there exist many situations to-day, particularly in the Armed Forces, where man is removed from his natural habitat and placed in some sort of container: the tank, the boiler room of a ship, and the cockpit of a high-speed aircraft are examples. The temperatures in these artificial environments may rise to levels much higher than those ever experienced outside in the open, and man's physiological defences, not planned for such contingencies, may be overwhelmed. It is therefore of vital importance to know: (*a*) The military situations in which high levels of heat stress may be expected, (*b*) in any one situation, the degree of protection required to reduce the heat stress to a safe level, (*c*) the way in which such protection is best achieved, (*d*) in the absence of protection, what is the danger to the man, and whether the dangers can be reduced to a negligible level by limiting the performance of the machine.

I shall examine these factors with reference to one particular situation—that of the military aircraft travelling at very high speed. However, the results are applicable to any closed space in which the temperatures reached are similar to those in our experiments.

The problem of aerodynamic heating.—When an aircraft travels at high speed, compression of the air and friction with the air cause surface heating of the aircraft skin. This effect is known as aerodynamic, or "kinetic" heating. It is seen in its most extreme form during the re-entry of a missile, whose surface may become incandescent, or of a meteorite, which may be completely burnt up by the intense heat.

If an aircraft flies at a speed of Mach 2 at 30,000 feet, its surface temperature will be in the order of 150° C. If the cabin is allowed to rise to this temperature, the crew will clearly soon suffer from the effects of heat.

The immediate solution to this problem is obvious and consists in conditioning the inside of the vehicle so that the levels of temperature, humidity and air movement are in the range of comfort. However, in a military aircraft the cooling plant responsible for maintaining the comfortable environment may fail, either because of enemy action or because of a technical defect. Failure of some component of the cabin cooling system is a problem which will occasionally face the civil airlines when supersonic aircraft become more common, but the civil airliner is able to slow down in the event of such a failure, thus removing the aerodynamic heat stress. The military aircraft may have to continue its mission in spite of the failure. Furthermore, in a military aircraft the weight and volume of cabin cooling equipment required to maintain comfortable conditions may be prohibitive, and the cabin may be deliberately designed to be a hot cabin.

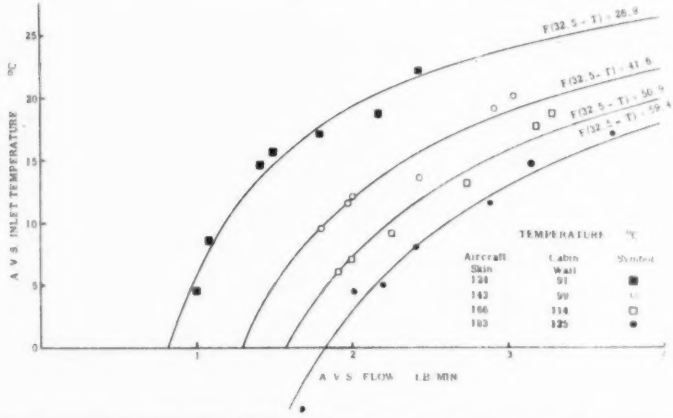

FIG. 1.—A.V.S. temperature-flow requirements to maintain mean microclimate temperature of subject at 32·5° C. for four different cabin wall temperatures.

The crew of a supersonic military aircraft may therefore require personal protection against the heat. We have recently carried out experiments to find out the degree of protection required in very hot cockpits for a man wearing an air ventilated suit.

Personal protection with the air ventilated suit.—The R.A.F. Air Ventilated Suit (Billingham and Phizackerley, 1957) consists of a network of pipes attached to a nylon garment. The suit is worn beneath the clothing and delivers cool dry air to the man's skin when he is in a hot environment. If the man is in a cold environment, he can be maintained in thermal equilibrium by a supply of hot air to his air ventilated suit. This paper considers the use of the suit only as a cooling garment.

To test the efficacy of the air ventilated suit under very hot conditions, we have used a portion of an aircraft, containing the pilot's cabin, which can be heated up to the temperature which corresponds to the speed and altitude we are simulating.

The subject is protected from the hot aircraft skin by: (*a*) The insulation of the cabin wall, (*b*) the insulation of the cabin air, (*c*) the insulation of his clothing, (*d*) convective cooling at skin level by the ventilated suit.

For a given aircraft skin temperature, and for constant values of (*a*), (*b*) and (*c*), there will be a number of possible combinations of ventilating air flow and temperature which will maintain the man at a comfort level. We have investigated these curves by using a suit of knitted insulated resistance wire (Wolff, 1958) beneath the air ventilated suit. This wire garment measures mean microclimate temperature. The results in the graph are flows and temperatures of ventilating air required to produce a mean microclimate temperature of 32·5° C. (Fig. 1).

The graph shows that the points lie close to the four isoenthalpic curves as defined by the formulæ in Fig. 1.

A detailed discussion of experimental procedure and of the significance of the results has been published elsewhere (Billingham and Hughes, 1959). Suffice it to say that with an aircrew clothing assembly that is almost conventional, it is possible to protect a man against the ill effects of extreme heat.

The consequences of not protecting against the heat.—Overheating of the body can be local or general. Local overheating causes pain and skin burns. General overheating is manifest as a rising deep body temperature, with increasingly poor performance at mental tasks, and ultimate collapse from acute heat syncope. Whether local or general overheating predominates will depend on a number of factors, principally the environmental temperature and the time of exposure. These factors will also determine the amount of local or general heating the man can stand without becoming dangerously inefficient at his task.

Conclusions.—To date, we have achieved protection for man in hot cabins with wall temperatures up to 125° C, and with the aircraft skin at temperatures up to 183° C. With careful design of aircrew clothing with built-in cooling devices, there is no reason in the future why we should not be able to protect against much higher temperatures.

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Flight Lieutenant J. C. Guignard, R.A.F.:

Physiological Effects of Mechanical Vibration

Authorities in both military and civil aviation are concerned that buffeting and vibration in future high-speed aeroplanes may prejudice aircrew performance and passenger comfort. Investigations of the physiological actions of vibration in the low sonic and infrasonic fre-

quency ranges have therefore been reopened at Farnborough.

Definition of vibration.—Vibration commonly means a sustained, structure-borne disturbance, of roughly constant amplitude and frequency, which applies a translatory movement to the body and is perceived by the senses other than hearing. Repetition of motion is usually assumed to be characteristic, and many real conditions of vibration approximate to simple harmonic motion. However, quasi-random oscillations and isolated jolts are special cases of vibration which are of great practical importance. Crede's (1957) definition of vibration as a series of reversals of velocity, while not embracing all conceivable modes, is a useful concept for the physiologist. Velocity means displacement in finite time: reversal of velocity implies acceleration. Displacement and its derivatives, and frequency, are basic to vibration measurement.

The dynamic response of the body to vibration.—Several workers have studied the dynamic response of men to whole-body sinusoidal vibration. Resonance in the human body was first described some thirty years ago and has since been measured by transmissibility and mechanical impedance methods. Resonance is the condition in which a forcing vibration is applied at such a frequency that it excites part of the body to measurable, or subjectively noticeable, movement of greater amplitude than related structures. Resonance of the seated body at about 5 cycles per second (c/s) has been widely reported. Recent work suggests that this response is dominated by the pectoral girdle (Latham, 1957). A second resonance between 6 and 10 c/s was attributed by German workers to the abdominal viscera, the liver being the predominant mass (Loeckle, 1950). At higher frequencies, smaller and stiffer parts of the body are excited to resonate.

Physiological reactions to vibration.—It has been recorded that severe vibration induces the vegetative manifestations of alarm, increases oxygen consumption, and can disturb equilibrium and orientation in space (Edwards, 1950; Loeckle, 1950). Cörmann (1940) has described an apparent inhibition of the patellar reflex during whole-body vibration at low sonic frequencies. Other work on this phenomenon has been reviewed and further observations reported elsewhere (Guignard and Travers, 1959). Cörmann also found that blurring of vision by vibration depended on frequency and that the effect was worst in the bands 25–40 and 60–90 c/s. This may be due to resonance of the eyes and facial tissues. A significant loss of visual acuity during whole-body vibration at infrasonic frequencies has been reported by Mozell and White (1958). In addition, it seems self-evident that heavy jolts and vibration interfere physically with precise muscular action. However, the frequency-dependence of these effects is not clear and the degradation of human performance by rough motion has not yet been correlated convincingly with body resonance phenomena. It is thought that physical resonance might cause particular incapacity or discomfort, due to parts of the body amplifying accelerations applied at critical frequencies. Recent studies of subjective sensation during whole-body vibration indirectly support this idea, in that thresholds of discomfort (in terms of applied acceleration) were lowest around 5 to 10 c/s (Goldman, 1957; Loach, 1958).

Postural effort is said to increase after bumpy journeys and body-sway has been used as an index of vehicle riding-quality (Moss, 1929). More recently, people exposed to intense airborne vibration from jet and rocket engines have complained of giddiness, irritability, mental weariness and inability to concentrate, as well as a variety of bizarre symptoms ranging from feelings of unreality to delusions of infertility. Disturbances of equilibrium are most probably caused by sound at the lower end of the frequency spectrum, where the coefficient of absorption of vibratory energy through the body surface becomes large (von Gierke, 1950) and vestibular sensitivity significant. In addition, components below about 1,500 c/s can produce blurred vision and unpleasant somatic sensations, due to resonance of cranial bones and body cavities (Edwards, 1950; Broadbent, 1957).

A discussion of motion sickness is outside the scope of this review, although it is of interest that labyrinthine sensitivity to very low frequency translatory oscillation is a function of frequency as well as acceleration. The incidence of sickness during vertical swinging at a given acceleration is highest at swing frequencies around 0·3 c/s (Alexander *et al.*, 1947; Glaser and McCance, 1959).

Harmful effects of vibration.—Frequency-dependent trauma caused by hand-held industrial machine tools is well documented (Dart, 1946; Jepson, 1954), but it is not relevant to aircraft vibration conditions.

During World War II reports appeared of injury due to severe whole-body shaking in rough-riding military vehicles and fast patrol boats (Goldman, 1957). Drivers and crews complained of abdominal pain, "back-strain", and sometimes of incapacitating fatigue and dizziness persisting after the ride. No precise clinical investigations of these symptoms seem to have been made, although the problem has been loosely reviewed by Clayberg (1949) and by Fishbein and Salter (1950).

In recent years, practical interest has arisen in the dynamic response of the body to impulsive forces. Seat-ejection, crash impacts, solid blast and other severe accelerations of short duration can be treated as special cases of transient vibration in which physical tolerance depends largely upon the frequency-response of body structures. In seat-ejection, for example, Latham (1957) has shown that, if the peak force of ejection is built up in much less than the predominant natural period of the excited system, dangerous amplification of acceleration can occur within it.

Current Research

Although the vibration-frequency spectrum is of infinite extent, the area that matters in aviation can be limited to a fairly narrow band. The principal sources of vibration in aircraft are summarised briefly in Table I.

Table I.—Principal Sources of Vibration in Aircraft

Source	Main frequency representation
(*a*) *Engines:*	
Piston engines and propellors; rotors	< 10– 1,000 c/s.
Jets	100–10,000 c/s.
Rockets	10–10,000 c/s.
(*b*) *Aerodynamic (boundary layer) noise*	Theoretically white.[1] Significant at sonic frequencies.
(*c*) *Meteorological turbulence* (gusts)	Theoretically white. Important mainly below 1 c/s.
(*d*) *Airframe:*	
Structural responses	Major modes 1–10 c/s.
Whole-aircraft oscillations (e.g. excited by turbulence or dictated by automatic flight control systems)	0·1–>1 c/s.

[1] "White" noise, by analogy with white light, contains vibrations of all frequencies. Ideally, it has a continuous and "flat" power spectrum in which components of all frequencies are equally represented. In practice the term is often used to describe wide-band noise in which no particular frequency component predominates.

In the situations now important (i.e. the rough-air behaviour of high-speed jet aeroplanes) we are most concerned with frequencies below about 20 c/s. Accelerations in turbulent flight resemble random mechanical noise with superimposed quasi steady-state vibrations at low frequencies, due to airframe structural response. The infrasonic zone is one in which both human body resonance and major aircraft fuselage modes are excited, amplitudes are large, and vibration isolation is very difficult. Mechanical vibrations at higher frequencies can produce neurophysiological and visual disturbances but are well attenuated by the body itself and by simple protective measures. The region below 1 c/s is a special province in which differential oscillatory movement is not excited in the body by moderate loads, and degradation of performance is essentially a function of acceleration.

Quick answers to practical problems are sometimes sought by *ad hoc* experimentation in the air or on "gust-simulators" which, within their limitations of amplitude, freedom and frequency-response, reproduce selected flight acceleration patterns (Roman *et al.*, 1959). It remains necessary, however, to determine the frequency-dependence of physiological reactions to vibration—since therein lies the key to protection. To do this, simple harmonic motion is the stimulus of choice. The use of sinusoidal vibration has the advantages that specific parameters of vibration can be chosen for investigation and the stimulus can conveniently be measured, repeated, modulated and defined in simple numerical terms. Some recent experiments are described below.

Body resonance.—The dynamic response of seated men to vertical sinusoidal vibration has been examined under controlled conditions at frequencies from 2 to 60 c/s.

Methods: In preliminary work (Guignard, 1959), the mean transmissibility of vibration from the seat to the hip and to the shoulder was determined for frequencies between 7 and 60 c/s, using seven men. The subjects were seated "at attention" on a hard seat driven vertically by an electrodynamic vibration generator. A simple sighting device was used to standardise their posture. The acceleration-amplitude during steady-state vibration was recorded by variable-inductance accelerometers attached to the seat-frame, the hip at the iliac crest, and the acromion. Above 16 c/s, vibration was applied at an acceleration of $\pm$ 0·8 *g*. Below that frequency, the performance of the generator deteriorated and lower values were used (Figs. 1 and 2).

Transmissibility was defined as the ratio of the acceleration-amplitude recorded on the body to that of the forcing (seat) vibration. (When transmissibility is plotted against frequency, resonance is shown by local maxima.)

The frequency limitations of the electrodynamic generator precluded measurements below 7 c/s. A mechanical rig is now in use to extend observations down to 2 c/s. In a second experiment (Guignard and Irving, unpublished), the response of ten men has been explored over the frequency band 2·0 to 13·5 c/s, which was sampled in quarter-octave steps. The experimental conditions were similar to those of Experiment 1, except that a forcing vibrational acceleration of $\pm$ 0·25 *g* was used at all frequencies. Recordings were made from hip, shoulder and head, but the analysis of results from the head is incomplete.

Results: The principal results of these experiments have been combined and illustrated in Figs. 1 and 2. The mean transmissibility, for each frequency used, is plotted with an indication of the standard deviation. The results for the shoulder (Fig. 1) show that there is a peak in transmissibility in the region of 4·8 c/s, at which

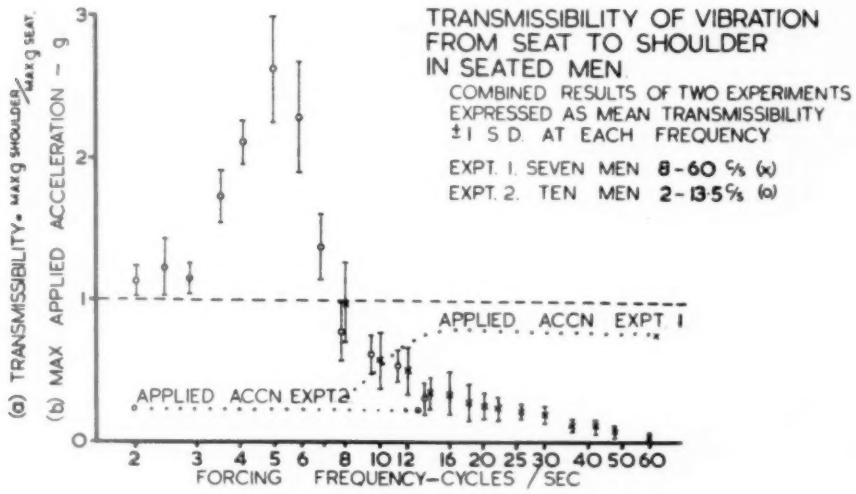

FIG. 1.

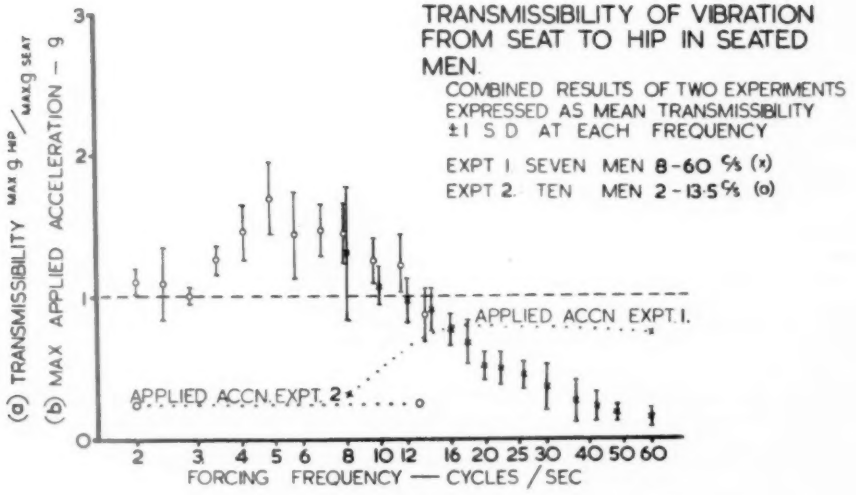

FIG. 2.

frequency the forcing vibration is amplified nearly three times. Above 7 c/s, seat-to-shoulder transmissibility falls below unity and declines in a characteristic way at higher frequencies. High-speed cinematography showed that the response of the shoulders is primarily a shrugging action, with articulation at the sternoclavicular joints, accompanied by extension and flexion of the dorsal spine. It has also been observed (and confirmed by determinations of transmissibility) that this mode is largely suppressed, and the body resonant frequency effectively raised, by performing the clinical reinforcement manœuvre.

The resonance at 4·8 c/s is reflected in the hip records (Fig. 2), which also show that amplification of vibration in this region persists over a higher frequency range. It is tempting to suggest that this picture reveals the second body resonance, previously reported, between 6 and 10 c/s. However, this resonance is not sharply tuned and more precise measurements are needed to define it anatomically.

Comparison of Figs. 1 and 2 shows that, at frequencies from 10 to 60 c/s, there is attenuation of vibration between hip and shoulder. Both curves reveal an inconspicuous local maximum

of transmissibility around 2·4 c/s, the significance of which is not yet clear.

Disturbances of posture.—During whole-body vibration at low sonic frequencies, a few subjects reported mild disturbances of equilibrium and some of them apparently found it more difficult than normal to maintain a steady posture. Mild vertigo has also been felt after local vibration of the head at frequencies between 10 and 100 c/s and accelerations of the order of 0·5 *g*. These observations, together with those of Cörmann and others mentioned earlier, led to examination of the electromyographic responses of postural muscles to low-frequency vibration. Qualitative observations have been made in man, using the R.A.F. Type 3 clinical electromyograph and concentric needle electrodes (Guignard and Travers, 1959). Sinusoidal vibration was applied to the whole body and to selected parts at frequencies from 2 to 10 c/s and a fixed half-wave amplitude of 0·33 cm. We found that: (1) Vibration of the seated body or a single limb elicited a synchronous stretch reflex from resting postural muscle (quadriceps) in that limb. (2) The amount of myotatic activity varied with the intensity of vibration and could be much reduced during whole-body vibration by restraining differential movement of the limb. (3) Diminution of the patellar reflex (elicited by tapping) was not observed during or after vibration up to 10 c/s. This supports Goldman's (1948) findings in the cat that, although suppression was demonstrable during vibration of the preparation above 30 c/s, it was less evident below that frequency and that, at progressively lower frequencies down to 10 c/s, an increasing proportion of tendon taps became effective in eliciting the reflex. It was concluded that "inhibition" of reflexes by vibration is apparent in that, when the stimulus is of sufficient frequency and amplitude, the muscle becomes, in effect, tetanic. Tendon-tapping then fails to provoke a distinct response. (4) Intense vibration of the upper body and head, with the legs fixed, had a facilitatory effect upon postural activity (soleus), persisting after vibration had ceased. It was tentatively concluded that this was due to labyrinthine stimulation.

Applications

Applied research is aimed at defining the frequencies at which body resonance occurs, as well as the variability of individual dynamic response. Measured transmissibility may vary with such intrinsic factors as body size, build and posture, and with extrinsic factors including the force of vibration, its direction and site of application to the body, and its harmonic content. External loading by stiff or heavy clothing and equipment may also influence body resonance.

If it is possible to correlate resonance effects with deterioration in performance, and to define physiologically critical frequency bands, practical advice can be given on vibration isolation for aircrew. Possible means of protection include: (1) Attention to the basic design of new aeroplanes to avoid or suppress critical modes of structural response. (2) Topical vibration isolation (e.g. the sprung seat). (3) Anatomical design of seats and harnesses to constrain resonant oscillations within the body.

Acknowledgments.—The vibrators used in these experiments were provided by the Dynamics Laboratory, Structures Department, Royal Aircraft Establishment. I also wish to thank Wing Commander P. R. Travers and Mr. A. Irving for allowing me to present some results obtained jointly with them.

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Squadron Leader J. Ernsting, R.A.F.:

Some Effects of Oxygen-breathing on Man

Over the past four years infrequent reports of coughing, chest discomfort and difficulty in breathing occurring after flight have been made by pilots of R.A.F. fighter aircraft. This presentation is concerned with the results of

surveys made in the last two years by medical officers in various Commands and with the ætiology of this condition, since it demonstrates how fundamental research is sometimes required to elucidate problems arising in the field.

Although there is some variation in the clinical picture the symptoms experienced by the aircrew are generally very similar. Typically, on releasing the safety and parachute harnesses and standing up in the cockpit the aircrew member has an attack of coughing and quite frequently difficulty in breathing, which is generally described as breathlessness. Less often there is also chest pain which is generally deep and ill-localized and which is not accentuated by deep breathing. In 107 subjects questioned coughing alone occurred in 38%, coughing and difficulty in breathing in 25%, difficulty in breathing alone in 20%, and chest pain with cough and difficulty in breathing in 17%. The cough, which is usually non-productive, is frequently started by the action of standing erect. It may last a few moments or repeated attacks may occur for ten to fifteen minutes after flight. The subject may actually be incapacitated by the fit of coughing. A single individual rarely has these symptoms after every flight but in many instances symptoms occur after the majority of flights.

Clinical examination has not revealed any gross physical signs in the chest. Moist sounds over the bases of the lungs have been reported on a number of occasions.

In 1958 28 fighter aircrew took part in an investigation in which chest radiographs were taken before and after a number of sorties. A total of 42 flights were made. On 19 occasions patchy areas of increased density in the lower lung fields were present immediately after landing. These radiological appearances are consistent with either scattered lobular collapse or areas of œdema or infarction. Several subjects with abnormal post-flight chest radiographs were re-examined radiologically eighteen to twenty-four hours after completion of the flight; in most of these the abnormal radiological signs had cleared. Whilst it was very uncommon for symptoms to occur in the absence of radiological changes, in 9 instances typical radiological changes were discovered when the aircrew had no symptoms.

In general this syndrome appears to be peculiar to the crews of fighter aircraft. Whilst nearly 80% of the pilots of Hunter aircraft experienced these symptoms, virtually no Canberra crews had any symptoms. Between these two extremes were the crews flying Javelins and Swifts of whom between 20% and 44% had post-flight symptoms. Aircrew flying Meteors very seldom suffer from post-flight respiratory disturbances.

There are three principal differences between these various aircraft types of interest in the present context: (1) The magnitude and duration of applied positive acceleration. (2) The presence or absence of anti-gravity suit installation. (3) The type of oxygen system.

(1) Pilots of Hunter aircraft during normal sorties are repeatedly subjected to relatively high positive accelerations, of the order of 4 to 5 *g*, whilst aircrew of Canberras are exposed to relatively low positive accelerations, e.g. 2·5 to 3 *g*, only rarely. The Javelin comes mid-way between these two extremes in that in its operational role high positive accelerations are applied very infrequently. In Meteor aircraft, however, moderate *g* levels of the order of 3 *g* are frequently applied to the aircrew.

(2) Certain fighter aircraft are fitted with anti-gravity suit installations so that when positive accelerations are applied to the man bladders fitted round his lower limbs and abdomen are inflated to reduce the circulatory changes associated with positive acceleration. The abdominal bladder of an ill-fitted anti-gravity suit, which is a frequent occurrence, will also apply pressure to the lower part of the thoracic cage. Anti-gravity suits are used by the majority of Hunter pilots and by a fair proportion of Javelin aircrew. Neither Meteors nor Canberras have anti-gravity suit installations.

(3) R.A.F. oxygen systems are designed to deliver a mixture of oxygen and nitrogen, the composition of which is varied automatically with altitude so that an approximately normal alveolar oxygen tension is maintained at all altitudes up to 33,000 feet. This is achieved by mixing varying proportions of air and oxygen ("airmix"). The Meteor possesses an oxygen system which has a satisfactory "airmix" mechanism. All the other aircraft mentioned above are fitted with an oxygen system capable of providing mixtures of air and oxygen but for technical reasons this type of system was used operationally to provide 100% oxygen at all altitudes, by the aircrew concerned.

Thus in Hunter aircraft, where post-flight respiratory disturbances are common, the aircrew are subjected to high positive accelerations and breathe 100% oxygen. In Canberra aircraft on the other hand, where this syndrome is virtually unknown, the aircrew breathe 100% oxygen but are not subjected to high positive accelerations during flight. Further, in Meteor aircraft, where the incidence of these symptoms is very low, the aircrew are exposed to moderate degrees of acceleration but breathe a mixture of air and oxygen. Thus it would appear that the incidence of this syndrome is high where the aircrew are exposed to high positive accelerations and breathe 100% oxygen.

This conclusion was confirmed by a series of controlled experiments conducted in Fighter Command in 1958 in which a number of pilots each flew two sorties. On each occasion the pattern of positive acceleration experienced was the same. On one of these sorties 100% oxygen was breathed throughout and on the other the mixture of air and oxygen provided by the regulator was breathed. It was found that, particularly at low altitude, the incidence of post-flight respiratory symptoms was influenced by the gas mixture breathed during the flight.

There is no clear-cut picture as to the influence of the anti-gravity suit in the air upon the incidence of this post-flight respiratory disorder.

Two principal hypotheses have been advanced to explain this syndrome of post-flight respiratory disturbances and the concomitant changes in the radiological appearances of the lungs. The change which occurs in the lungs in this condition could be either basal segmental collapse or pulmonary œdema or infarction.

Segmental collapse could be produced by the following mechanism: During the application of positive acceleration in flight collapse of some basal intermediate-sized airways occurs. This may be caused either by the effects of the acceleration *per se* which produces descent of the diaphragm and elongation of the lower parts of the lower lobes or by the compression of the lower part of the chest by the inflation of the anti-gravity suit. Directly obstruction of these airways has occurred absorption of gas with a consequent reduction in the volume of the closed spaces so formed will take place. Dale and Rahn (1952) have demonstrated that if the gas breathed prior to the onset of obstruction is oxygen then the rate at which absorption of the trapped gas occurs is some 63 times as fast as when air has been breathed. When oxygen is breathed the rate of absorption is so great (2·9 ml/min/kg body weight) that it is conceivable that complete lobular collapse can occur during the period that positive acceleration is applied.

Segmental collapse of the degree found here is not generally associated with symptoms. It is suggested that the symptoms of coughing, difficulty in breathing and chest pain are associated with re-aeration of the collapsed regions of the lungs. The stimulus to re-aeration of the collapsed regions in this syndrome is presumably the assumption of the erect posture on leaving the seat of the aircraft. Carro (1959) and McIlroy (1959) have recently studied the effects upon the mechanics of respiration of firmly strapping the lower part of the thoracic cage. It is of interest in this connexion that on release of the strapping their experimental subjects experience coughing and chest discomfort.

The second hypothesis suggests that as a result of a high alveolar oxygen tension the alveolar capillary membrane is damaged and that it becomes more permeable to plasma proteins. The increase in pulmonary capillary pressure in the lower parts of the lungs which occurs when positive accelerations are applied will then lead to pulmonary œdema and perhaps infarction. The relatively slow re-aeration of the lungs which has been suggested by some of the radiological studies would be better explained by this hypothesis. There is recent experimental evidence that breathing 100% oxygen at sea level for three hours produces changes in the pulmonary alveolar capillary membrane.

The effect of a high alveolar oxygen tension upon the alveolar capillary membrane has been studied by determining its effect upon the diffusing capacity of the lungs. This has been measured for carbon monoxide by the Forster modification (Ogilvie *et al.*, 1957) of the original Krogh technique. Breathing 100% oxygen for three hours reduces the apparent diffusing capacity for carbon monoxide by approximately 25%. The apparent diffusing capacity was measured at various alveolar oxygen tensions so that the analytical technique of Roughton and Forster (1957) could be applied. The results of such an analysis show that the principal cause for the reduction in the apparent diffusing capacity found in these experiments is an increased resistance to diffusion across the alveolar capillary membrane. The results suggest therefore that high alveolar oxygen tensions cause damage to the alveolar capillary membrane at a much earlier stage than had been previously believed. These experiments tend to support the second hypothesis as to the cause of this syndrome.

There still remain many aspects of this problem which must be investigated before it can be decided which, if either, of these two hypotheses is correct. There is no doubt, however, from the controlled experiments carried out in 1958 that the symptoms can be greatly alleviated by using the "airmix" mechanism of the oxygen regulators in fighter aircraft.

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Squadron Leader P. Howard, R.A.F.:

Unconsciousness on the Human Centrifuge

The symptoms which result from exposure to centrifugal acceleration are, in the order of their appearance, a veiling or misting of vision, known as grey-out; complete loss of vision, or black-out; and unconsciousness. It was to investigate these symptoms, and to assess methods of protection against them, that the first human centrifuges were constructed. Most workers are agreed that the repeated production of unconsciousness in any subject is undesirable, and because most of the desired data can be obtained without going to such lengths, there has been a tendency to restrict the acceleration to a level which will only give rise to black-out. Recently it has been felt that even a stress of this degree may be unjustified in many instances, and attention has been given to the development of methods of measuring a visual threshold at lower values of *g*. However, incidents of unconsciousness still sometimes occur accidentally, and a series of experiments in which unconsciousness was deliberately chosen as the end-point was carried out last year on the human centrifuge at Farnborough.

Material and Methods

The subjects were seven naval divers who had no previous experience of riding on the centrifuge. Each was given two rides; one breathing air, and the other breathing 100% oxygen, until consciousness was lost. The pattern of the acceleration was such that the *g* increased linearly with time, at a rate of 0·1 *g* per second to a maximum of 8 *g*. This type of run was chosen because it had previously been shown that cardiovascular compensation kept pace with the increasing acceleration. A bright red light, mounted at eye level and in the line of sight, was used as a fixation light, and the subject was given a signal button to indicate black-out. He was told that once loss of vision had occurred he was to keep the button pressed until it returned once more. The onset of unconsciousness was thus unknowingly recorded by the subject as his finger slipped from the marker button. The centrifuge was brought rapidly to rest as soon as this signal had been recorded. The figure of 8 *g* was chosen as being well above the tolerance of any of the usual and experienced centrifuge subjects, and it was thought that none of the divers would reach this maximum value. In fact, half the subjects did reach it, and continued at 8 *g* for some seconds before they finally lost consciousness, and all but one reached 7 *g* on at least one of the runs. The record was 48 seconds at 8 *g*.

In addition to the accelerometer and the signal, ECGs and EEGs were recorded, together with respiratory rate, gas flow rate, and in some cases eye movements. In half the subjects blood pressure was also measured by means of an intra-arterial needle, and in one of these the artery and the manometer were supported at eye level. From the arterial pressure, measurements of the vascular resistance could be made by the method of Hayter and Sharpey-Schafer (1958).

Results

There was no statistically significant difference in the threshold either for black-out or for unconsciousness between the runs in which air was breathed and those breathing oxygen.

Four subjects showed a slight fall in threshold on oxygen as compared with air, two showed a slight rise and one showed no difference. Similarly, there was no consistent difference between the effect of the two gases on any of the other parameters measured. Clearly, a much larger number of subjects would be needed before definite conclusions could be drawn on this point.

The early physiological response of all the subjects was the same, and was similar to that seen in the more usual type of centrifuge run. The major difference between the group of divers and other subjects was in the pulse-rate. Browne (1959) showed that with slow rates of application of *g* the pulse-rate is a linear function of the applied acceleration, but in the present series this was not so. The pulse-rate increased rapidly at first, and was almost double the resting value at 3 *g*. Thereafter it climbed more slowly to a mean value of 168 at 8 *g*. This result can almost certainly be explained by the apprehension which the centrifuge always produces in inexperienced subjects.

Respiration becomes more difficult during acceleration, and this is reflected in the decreased gas flow recorded, notably at levels above 6 *g*. As the subjects approached unconsciousness there was a period of apnœa in almost every case, usually lasting for about 10 seconds. On deceleration this was followed by large gasping breaths, with high peak flows and large pressure differentials in the mask.

No unusual changes occurred in the EEG up to the moment of unconsciousness, but slow delta waves of large amplitude (2–3 c/s and 100 microvolts) usually appeared immediately after consciousness had been lost. The picture was confused by the fact that at this time the centrifuge was being decelerated, and it would be interesting to know whether, had the run been continued, extinction of the waveform would have followed, as has been reported in animal experiments. During the recovery phase, often after the machine had been brought to rest, convulsions occurred. This is a characteristic of nearly all episodes of unconsciousness on the

centrifuge. The fits vary in intensity from a spasmodic twitching of the fingers and arm to a major convulsion involving the whole body. One subject, who has been made unconscious on the centrifuge many times, says that he is always roused by the sound of his feet drumming on the metal floor of the gondola. The convulsions have been attributed to the acute cerebral anoxia resulting from the cessation of blood supply to the brain, and they have been compared to the fits seen if the carotid arteries are occluded. The fact that they do not occur at the height of unconsciousness, but only during the phase of recovery, suggests that it is the return of oxygenated blood to an anoxic brain which triggers off the convulsion. In this they are analogous to the so-called oxygen paradox, in which the administration of oxygen to a subject made anoxic in a decompression chamber will often lead to a deterioration in condition, and sometimes to convulsions.

The blood pressure records taken at heart level showed a slight rise in all cases. The arterial pressure at eye level fell progressively, to reach a systolic value of about 20 mm Hg when blackout occurred. It continued to fall, and reached zero about six seconds before consciousness was lost. There is thus a very sound physiological reason for the onset of unconsciousness. One case in which the pressure was measured at eye level also showed the only cardiac irregularity of the series: some three seconds after the systolic pressure had fallen to zero, and a similar time before the loss of consciousness, he had an isolated ventricular extrasystole. American workers have claimed that a considerable proportion of normal subjects show such irregularities on the centrifuge, but this is only the second occasion on which we have seen ectopic beats. Coincident with the loss of consciousness this one subject showed a persistent pulsus bigeminus, with bradycardia, and this continued for about two minutes after the centrifuge had been stopped. The coupling was followed by a period of nodal rhythm, with absent P-waves, for ten or fifteen minutes, and the pulse finally reverted to a normal sinus rhythm. The subject complained of weakness, palpitation and dizziness, with nausea, and he was observed to be pale and sweating profusely. The blood pressure remained low, and had not reached normal levels by the time the needle was withdrawn at the end of the run. No measurements of the vascular resistance could be made in this experiment, but there seems to be no doubt that he suffered from vasovagal syncope.

In all cases the peripheral resistance rose sharply and progressively during the period of acceleration, and in two runs it was so intense that it could not be measured, by the method used, at accelerations greater than 6 *g*. Deceleration was accompanied by a mild vasodilatation. In two instances, however, the vascular resistance had already begun to fall steeply before the centrifuge was decelerated, and the blood pressure was also declining at this time. It seems likely that these subjects were also in the process of collapsing from a vasovagal attack, and it is of interest that they were the two who had remained for the longest time at 8 *g* before losing consciousness. There is every reason why vasovagal syncope should occur under these conditions, for the circulating blood volume is reduced by pooling in the abdominal viscera and legs. Garrow (1958) has shown that there is a shift of blood amounting to 200 ml towards the legs below the knee when a recumbent man is exposed to 2 *g*. He has also convincingly demonstrated his ability to faint after two minutes at 2·4 *g*. The slow onset run used in the experiments with the divers, and the fact that some of them were subjected to 8 *g* for a relatively long period of time, would give ample opportunity for a vasovagal type of syncope to develop.

There would thus appear to be two types of unconsciousness occurring on the human centrifuge. The first results from an acute cerebral anoxia, caused by the failure of the blood pressure at brain level. It is similar in many respects to the unconsciousness produced by sudden bilateral occlusion of the carotid arteries, or to that resulting from the inhalation of an inert gas. The second form is strictly analogous to the well-known postural fainting, and it is a circulatory, rather than a purely cerebral, collapse. Which type will occur depends largely on the time-course of the centrifuge run. The sudden application of high accelerations will produce acute cerebral anoxia in a few seconds, while slower rates of application, or a long sojourn at a lower peak acceleration, will give rise to circulatory embarrassment and syncope. Individual susceptibility will also influence the outcome in marginal cases. It seems certain that in the experiments described both types of unconsciousness were seen.

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Anæsthesia in Abdominal Surgery—Yesterday and To-day [*Abridged*]

PRESIDENT'S ADDRESS

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Fifty years ago the anæsthetist was presented with similar problems to those which beset us in 1959. Abdominal relaxation was one of them. Blumfeld (1903) in a discussion before the Society of Anæsthetists held in 1902, stated that lack of abdominal relaxation was due to faults in administration and to abnormalities in the patient. Among the former were included lack of a free airway from inefficient holding of the jaw, lack of a free supply of air with the anæsthetic, and excessive respiratory vigour from inadequate depth of anæsthesia. Abnormalities of the patient included a narrow costal arch (even in those days costal cartilage would not yield to the surgeon's will), reflex contraction of the recti due to underlying inflammation, and excessive excitability of a reflex nature in neurotic and nervous patients.

As a house surgeon in the late 1920s in the clinic of Professor Grey Turner, I watched anæsthesia induced with ethyl chloride, chloroform or the alcohol-chloroform-ether mixture. Ether was used for maintenance, poured on to a Schimmelbusch mask, and the state of delirium associated with the early stages of anæsthesia required the presence of at least one member of the strong-arm brigade to keep the patient on the trolley. Relaxation was always a problem. If the patient was considered to be too ill for general anæsthesia the professor himself administered a spinal anæsthetic using Stovaine according to Jonnesco's technique (1909). The anæsthetist had none of the modern aids to anæsthesia which we now think indispensable such as endotracheal tubes, gas machines, suckers, and intravenous drugs, but he enabled his surgeons to do quite elaborate operations such as gastro-enterostomies, explorations of the common duct and excisions of the rectum. The post-operative condition of the patients was definitely not as good as it is to-day. We did not stimulate our patients to cough up their secretions, wrongly thinking them to be due to bronchitis or pneumonia caused by irritation of ether vapour. Nausea and vomiting were common, though even to-day we have not conquered this serious problem.

The deadly dangers which can accompany the aspiration of stomach contents during induction and maintenance of anæsthesia were ill understood, and morbidity and mortality from these accidents were seen then as now. The slow induction, however, was sometimes a blessing in disguise as the laryngeal reflex was preserved until quite late.

Endotracheal Anæsthesia

One of the greatest advances in technique was the introduction of endotracheal anæsthesia. Before it, the patient's airway was always an uncertain quantity so that minor or even major degrees of respiratory obstruction were frequent and, when due to laryngeal spasm, most difficult to remove.

The war of 1914–1918 left many patients requiring surgery in the post-war years, much of it dealing with the head and neck. It was this problem which stimulated our great English colleagues, Ivan Magill (1920) and Stanley Rowbotham (1920) to carry forward the infant technique brought to England by Robert Kelly of Liverpool in 1912, until it reached the healthy maturity and almost universal application, at any rate in abdominal surgery, with which we are familiar to-day.

There are those who think that intubation is employed too frequently in the 1950s (Koontz, 1959) and there are certainly many abdominal operations where the insertion of a tube is not strictly necessary. Nor would I personally subscribe to the opinion that an endotracheal tube should be passed just because a technique employing assisted or controlled respiration is being used, or because a muscle relaxant has been injected. One can safely and efficiently inflate the lungs of a patient without a tube being

in place, especially if the operation is not a long one. On the other hand, I consider the presence in the trachea of a cuffed tube to be necessary in every case in which the surgeon may explore the upper abdomen, for gastric contents may be expressed up the œsophagus into the pharynx, and trickle into the lungs unless stopped by an inflated balloon.

We are all familiar with the performance of endotracheal intubation, but even in the most expert hands difficulties are occasionally met with. We all have our favourite laryngoscope, and bitter are the arguments sometimes heard when different ones are compared; it seems that the curved blade designed by Sir Robert Macintosh (1943) is slowly drawing ahead in popularity. Incidentally, why is it so difficult to obtain a laryngoscope specially designed to be inserted into the left side of the mouth? There are a few patients whose dental anatomy makes this a safer approach.

I am sorry to see the technique of blind nasal intubation disappearing from the repertoire of the young anæsthetist. Time was when it might take twenty minutes to obtain with ether, sufficient relaxation to make the insertion of a laryngoscope both easy and free from trauma, and under such conditions the short cut provided by blind intubation was a great boon to the anæsthetist, surgeon and even patient. Our use of relaxing agents now makes visualization of the larynx relatively easy in the great majority of our patients. Occasionally, however, the anæsthetist meets an individual with such firm, strong and protuberant teeth, or such rickety, carious or wrongly pointing ones, that he hesitates to use a laryngoscope or, using it, fails to see the cords.

It is in such patients that blind intubation may still find a place. It well may be that even the trauma produced by a new cuffed tube as it is gently inserted into the cocainized and well-lubricated naris and nasopharynx will be less resented by the patient than the breakage of a tooth or the dislocation of a bridge or filling. Certainly the results of the trauma are likely to be recovered from more quickly. But in order to pass a tube blindly through the nose, the anæsthetist must be reasonably familiar with the technique, and that is why it seems to me that it should not be neglected when teaching young colleagues. Once familiarity with the method has been acquired, it is possible in the great majority of patients to slip a tube from the nose into the trachea after injecting intravenously about 200 mg of thiopentone followed by 25 mg suxamethonium. The relaxant takes the tone out of the cords, prevents them from going into spasm and, in the small dose used, spontaneous respiration very soon returns to help the tube into the glottis, if it has not already been placed there during the brief period of apnœa. This is not a plea for frequent blind nasal intubation; it is a suggestion that what is still a most useful method should not be forgotten.

Controlled Respiration

Further control of the patients' reflexes was brought about by the method of controlled apnœa under anæsthesia, first described by Guedel and Treweek (1934), using ether. Like many other innovations, little notice was taken of this radical departure from the usual, until Guedel's paper was published in 1940, and Nosworthy's equally important contribution reported in the *Proceedings* of this Society in the following year (Nosworthy, 1941). Controlled breathing became technically easy when cyclopropane made its appearance in the late 'thirties, and it was very often necessary to employ the technique if adequate abdominal relaxation was to be obtained when cyclopropane was the chosen agent. In my own practice cyclopropane has given me far more anxiety than have relaxants when re-establishing normal breathing after operation. I do not think that cyclopropane is used alone very often to-day to produce full muscular relaxation, as safer and better methods are available. The employment of the gas served a useful purpose, however, in making anæsthetists familiar with controlled respiration, a method which came into its own in the years following the description of the myoneural blocking effects of curare by Griffith and Johnson (1942). Most anæsthetists to-day believe that it is difficult to get really good relaxation of the anterior abdominal wall, at least in its upper part, when a relaxant is used, without depressing the respiration to such a degree that controlled respiration is necessary. Assisted breathing still has its advocates (Foldes, 1957) who believe that if activity of the respiratory centre is never completely abolished, irreversible apnœa cannot occur, so that prolonged apnœa is impossible. It must, however, be mentioned that prolonged respiratory inadequacy may still be a danger after operation even when assisted breathing is used.

Regional Analgesia

In the first two decades of the century, the standard of administration of general anæsthetics often left a great deal to be desired, and this stimulated surgeons, especially those in Germany, France, Austria, Hungary and Switzerland, as well as those in Great Britain and the United States to explore other avenues of pain relief. The problem of successful splanchnic block

eluded these early workers for a long time. Finsterer partially solved this problem by infiltrating the roots of the mesenteries in 1912 (*see* Finsterer, 1923) and later in the same year adopted true paravertebral conduction analgesia as described by Läwen (1910). Läwen realized that if he kept his injections near to the exit of the spinal nerves from the intervertebral foramina, he would block the rami communicantes containing the visceral afferent fibres from the contents of the abdominal cavity. In 1918 Kappis introduced his posterior splanchnic block, which made the abdominal viscera insensitive to traction and enabled the surgeon to dispense with light general anæsthesia during intra-abdominal manipulations. Posterior splanchnic block, however, soon showed itself to be far from the answer to painless surgery. Its dangers included subarachnoid and intravenous injection, so that Braun's anterior method replaced it in 1919 (Buhre, 1920). Meanwhile Läwen was experimenting with extradural block, introduced via the sacral hiatus. An additional refinement was the technique described in 1922 by Seidel and Baruch who introduced 500–600 ml of 0·5% procaine solution into the peritoneal cavity, to block the visceral nerve endings. Abdominal field block achieved some popularity but was later rivalled by the bilateral intercostal nerve block advocated in the excellent book written by Norman James (1941) during the last war. Interest in these techniques was to be short-lived, for soon afterwards curare burst on the anæsthetic world and went far to solve the problem of muscular relaxation.

How does the anæsthetic world regard these regional techniques in 1959? I should say that in most clinics, little use is found for them though occasionally they may be indicated. By their use it is easy to dispense with controlled breathing and simultaneously avoid volatile agents which are sometimes regarded as too toxic for ill people. It is surely wise to regard regional techniques as a useful addition, to be used on specially indicated occasions.

It has sometimes been argued that there is a place for some form of regional analgesia to supplement the very light anæsthesia with nitrous oxide, oxygen and relaxant which many employ. It is believed by some workers that impulses from the viscera should be interrupted by properly placed local analgesic solutions. Here we see the shadow of Crile (1913, 1920). Such techniques as extradural block, anterior splanchnic or vagal block or intraperitoneal procaine spring to mind (Loder, 1957).

Spinal Analgesia

Spinal analgesia must always be considered when discussing pain relief in abdominal surgery. Only the occurrence of post-operative headache, and the very rare lesions of the cord and its meninges prevent it being one of the most popular methods to-day. All who have used it agree that it gives excellent results, even when compared with muscle relaxants. Why are serious sequelæ referable to the central nervous system still occasionally seen? We do not know, and until we do anæsthetists will continue to feel slightly unhappy about using the method as a routine.

However, other methods of pain relief are also occasionally followed by untoward complications. Spinal analgesia still has its warm supporters such as C. B. Morton (1959), Professor of Surgery at the University of Virginia, who describes 6,500 of his own cases over a period of twenty-nine years, and I. S. Ravdin (1959), Chairman of the Board of Regents of the American College of Surgeons, who says that spinal analgesia provides the best operating conditions and is the safest anæsthetic for intra-abdominal operations. As with many other techniques and methods, feelings with regard to it range from bitter hostility and personal abuse, through distaste and resignation to enthusiasm, but I would not like to exclude it entirely from my practice, and it is my opinion that if every attention is paid to asepsis and a meticulous technique, serious harm is unlikely to result. I would like to see it regarded with what might be described as sympathetic impartiality.

Extradural Block

It is because of the excellence of this form of analgesia that many workers have now given up spinal analgesia.

To-day, extradural analgesia has its devotees who claim for it all the good results which have long been known to follow subarachnoid block, with few of the disadvantages. A well-relaxed abdomen, moving quietly with the patient's spontaneous respirations, with absence of distension of the intestine, and ischæmia which is controllable . . . these are the factors which make the method very acceptable. We have found it most useful for all major gynæcological operations both perineal and abdominal; for lumbar sympathectomy, nephrectomy, and the surgery of the colon and rectum, for hernias, prostatectomies and for some upper abdominal surgery. It is important to avoid large volumes of solution in the elderly and handicapped, and it should be the invariable rule to have an opening into a vein established before the block is induced, so that sudden hypotension or drug toxicity, which occasionally occur, may be dealt with expeditiously. The possibility of total spinal analgesia must always be borne in mind, but this need not cause

trouble provided the anæsthetist knows what to do, and is fully alive to the situation.

Nearly all our patients who receive an extradural block are asleep during the operation. When the intervention is on the lower abdomen we usually give intermittent doses of soluble hexobarbitone preceded by 25 to 50 mg of pethidine. This enables the patient to snooze comfortably while on the table and at the same time react to light stimuli such as face-patting, before he returns to the post-operative observation ward. When the surgeon is likely to explore the upper abdomen, we prefer to have the patient intubated. He can then breathe a gas-oxygen or an oxygen-halothane mixture spontaneously throughout the operation, or respiration can be assisted, if the minute volume is decreased.

Serial injections through a nylon catheter placed in the extradural space through a Tuohy needle allow prolonged analgesia and avoid the one-shot injection of a volume of solution which may be too large or too small. Complications of the block are reported occasionally but are possibly no more frequent than those following general anæsthesia.

It seems to me that extradural analgesia is most satisfactory to surgeon, patient and anæsthetist and in properly selected cases gives results as good as those obtained by other techniques.

The Position To-day

What kind of general anæsthesia is commonly used to-day for abdominal surgery? It seems that anæsthetists are divided into two camps; those who believe that their patients should be what they call properly anæsthetized, and those who are happy as long as the patient shows no sign of pain, even though only receiving such weak agents as nitrous oxide and oxygen.

It is most difficult to measure the effects of surgery and of anæsthesia, so that our views are more akin to prejudices than to scientific opinions founded on well-attested data. On the one hand there is the technique which employs the smallest sleep dose of an intravenous barbiturate, or none at all, together with gas-oxygen and a relaxant in such doses that all reflex response is blocked on the efferent side, a technique first described in 1946 by Harroun *et al.* In addition more or less hyperventilation may be employed as a deliberate part of the method. On the other hand there are the workers who give a larger dose of barbiturate for induction of anæsthesia, with additional doses throughout the operation, and pethidine, cyclopropane, halothane, trichloroethylene or ether to supplement the gas and oxygen, and much smaller amounts of relaxant than are used in the other technique. After the first method the employment of neostigmine will be almost routine. This has certain rare ill effects on the heart but the work of Hunter (1953) and of Morton and Thomas (1958) has helped to clarify the position. It would appear that cardiac effects of a serious nature are very unlikely if 1·3 mg of atropine is given intravenously, either before or along with a small dose of neostigmine which can then be repeated at frequent intervals until 2·5 mg have been given or until depression is overcome; always remembering that a dose of more than 5 mg may cause a depolarizing block on its own account. By this means, dangerous bradycardia can be avoided. In operations taking a short time, full relaxation can be provided by the use of suxamethonium either as a drip or by repeated injections. Properly managed, both groups of patients can be made to appear fairly spry on the operating table soon after the termination of the operation.

Nitrous oxide is probably the ideal agent for the production of light narcosis, although a 3% mixture of ether vapour in air which can easily and economically be provided by the E.M.O. ether inhaler may run it close, and may combine slightly deeper narcosis with little increase in toxicity (Epstein and Macintosh, 1956).

In recent years doubts have been expressed about the efficiency of nitrous oxide with enough oxygen in providing perfect amnesia and freedom from pain during the operation, when no other narcotic or analgesic agent has been used. Thus many workers have thought it advisable to give an intravenous analgesic such as pethidine in addition. Provided that sufficient relaxant is given to prevent all muscular movement, it is my clinical impression that pethidine is unnecessary, although I would agree that it seldom does serious harm if its dosage conforms to the rules. It is always pleasant to have one's clinical impressions backed by laboratory findings and in this connexion Gray (1954) has described experiments showing that a 50/50 nitrous oxide-oxygen mixture will induce and maintain sleep once nitrogen is eliminated.

I am certain that one of the most troublesome reflexes, hiccup, can be more readily controlled by large doses of relaxants than by any other method. It certainly seems to be a reflex which yields more effectively to efferent, than to afferent block, so that for this reason alone my own preference is for maximal relaxant and minimal narcotic, together with hypocapnia from hyperventilation, and gas-oxygen. Using this technique, I find pethidine and its congeners quite unnecessary, while intravenous barbiturate is confined to the small induction dose and is not repeated during

the operation; all muscular reflex response is controlled by additional relaxant.

Many anæsthetists believe that hyperventilation reduces the amount of barbiturate and relaxant drugs needed to give good operating conditions, a belief which has received experimental support from Dundee (1952) and Clutton-Brock (1957). We are thus not certain if we are doing our patients any harm by hyperventilating them, but clinical observation would tend to show that no ill effects are produced.

It is interesting to note that physicians and anæsthetists who deal with patients suffering from various forms of respiratory insufficiency are not greatly impressed by the ill effects of hyperventilation, which is sometimes produced by their artificial ventilating machines. Walley (1959), for example, states that for various reasons he has overventilated patients for considerable periods to the extent that their arterial carbon dioxide tension fell from a normal of 38/42 to 20/30 mm Hg and that they showed no abnormal signs or symptoms.

Additional support for the view that a reduction in the CO_2 tension consequent on hyperventilation is a useful and justifiable aid to safe anæsthesia, is given by Geddes and Gray (1959). It has been suggested that a low CO_2 tension depresses the function of the mesencephalic reticular substance which by its peripheral connexion with the cortex normally maintains the state of consciousness (Bonvallet and Dell, 1956).

There is, then, some scientific justification for the undoubted clinical fact that, in abdominal anæsthesia, patients do very well indeed if they are made apnœic with a relaxant, and then hyperventilated with gas and oxygen. Such patients require a minimal amount of thiopentone, no more than the initial sleep dose of 100 to 250 mg or even none at all. They must, however, be given enough relaxant to prevent all efferent response to the surgical stimuli throughout the operation.

There will be those who dissent from some of the things said in this Address, but over the years a practising anæsthetist comes to hold certain opinions which may be described either as principles or as prejudices according to the viewpoint, and these I have had the privilege of setting down in this paper.

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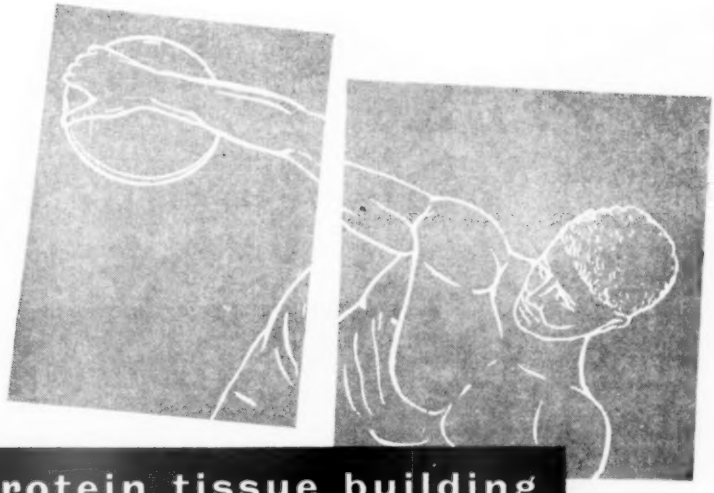
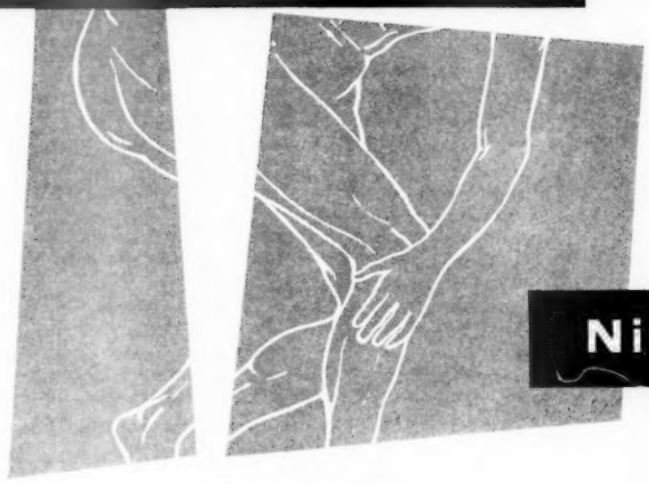


Protein tissue building



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NV : P39

Section of Epidemiology and Preventive Medicine

President—Air Marshal Sir JAMES KILPATRICK, K.B.E., C.B.

Meeting
October 16, 1959

Meteorological Conditions and Mortality [*Abridged*]

By J. T. BOYD, M.B.

London

THE relationship between meteorological conditions and mortality has long been a source of interest and speculation. Several studies have demonstrated the close association between temperature and mortality, and recently the London fog disaster of 1952 has focused attention on the effects of air pollution.

This investigation is concerned with the relationships between mortality, particularly respiratory mortality, and meteorological conditions and atmospheric pollution, both in an urban environment, London Administrative County, and a rural one, East Anglia. The basic data were supplied from official sources. For the London area it was possible to make weekly indices of mortality, temperature, absolute humidity, sulphur dioxide pollution and smoke pollution, and for the East Anglia area comparable indices of mortality, temperature, humidity and fog. The analysis was restricted to the winter months of the years 1947 to 1954, each winter being arbitrarily defined as the twenty-six-week period centred around the end of one calendar year and the beginning of the next. Thus seven winters were analysed.

Correlation coefficients were calculated separately for each winter and an overall picture obtained by averaging these correlations rather than the basic data. Weekly deaths were correlated with meteorological and pollution factors in the same week and in each of the preceding six weeks.

Results

London Administrative County.—The indices most closely associated with mortality were those of temperature (Table I) and absolute humidity. Correlating weekly deaths, at 45 years and over, with temperature of the same week yielded a coefficient of −0·5. This rose sharply to −0·7 when mortality was related to temperature of the immediately preceding week, and gradually declined thereafter when correlated with temperature of successively earlier weeks. The humidity correlations presented an exactly similar pattern and it was evident that the interdependence between these two variables prevented any discrimination as to their relative importance. For both, the close association with mortality was equally evident for respiratory and heart disease, and the pattern of peak correlations with climatological indices of the weeks immediately preceding death was maintained when deaths in older (over 65 years) and younger (under 1 year) age groups were examined separately. However, the levels of coefficients attained were lower, approaching −0·5, in the very young age group.

In contrast, the correlations between mortality and sulphur dioxide or smoke pollution were lower, +0·5 and +0·4 respectively, and no definite peak values were obtained in relationship to the six preceding weeks. A limited partial analysis confirmed this lesser degree of association and suggested that, of the two pollution indices, sulphur dioxide was more closely associated with mortality, particularly respiratory.

Rural districts of East Anglia.—In the rural area, the relationships between weekly deaths from cardiorespiratory disease and temperature and humidity were essentially similar to those in London. In particular mortality was again most closely associated with temperature and humidity indices of the immediately preceding weeks, gradually declining from a peak of around −0·7 when related to indices of earlier weeks. It appears that the urban atmospheric pollution, absent in East Anglia, has little effect on the general association between temperature, or humidity, and mortality.

TABLE I.—LONDON ADMINISTRATIVE COUNTY

Average correlation between weekly deaths from cardiorespiratory disease, at 45 years and over, and related temperature indices.

Temperature relating to	Weekly deaths at 45 yr. and over from		
	Bronchitis and pneumonia	Bronchitis	Heart disease
same week	−0·499	−0·538	−0·552
week-1	−0·720	−0·727	−0·744
week-2	−0·719	−0·694	−0·688
week-3	−0·668	−0·638	−0·553
week-4	−0·640	−0·620	−0·559
week-5	−0·628	−0·604	−0·554
week-6	−0·580	−0·559	−0·519

Mortality trends in rural and metropolitan fogs.—Visibility data were used to assess the relative effects of fog in the two environments. In each area weekly mortality figures were grouped according to temperature conditions of the week preceding death, and then subdivided within each temperature grouping according to the number of hours of related fog (i.e. visibility of less than 440 yd). It is apparent that in East Anglia there was no definite association between mortality and visibility under constant temperature conditions (Fig. 1). In each of the different temperature ranges, mortality levels were unaffected by variation in the number of hours of fog. The London data, on the other hand, showed a marked association between fog and mortality during very low temperature conditions. Thus at temperature indices below 32° F, the weeks with the highest fog rating had an average bronchitis mortality three times greater than for those weeks with the lowest fog rating, and deaths in the combined cardiorespiratory group were almost doubled. With slightly higher temperatures a mortality gradient with fog remained evident for deaths from bronchitis, but above 36° F this association disappeared for both respiratory and heart disease. It appears that the more serious effects of metropolitan fog, as measured by excessive increases in mortality, occur only when fog is accompanied by very low temperature conditions, a finding consistent with the conclusions of Russell (1924) from a long-term study of mortality in two London boroughs.

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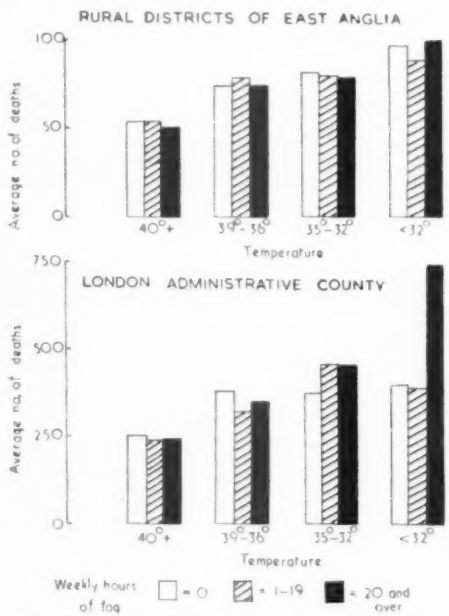

FIG. 1.—Average weekly deaths from cardiorespiratory disease, at 45 years and over, related to temperature and fog indices of the preceding week.

Meeting
November 20, 1959

DISCUSSION ON TOXOPLASMOSIS

Professor C. P. Beattie (Sheffield):

Epidemiology of Toxoplasmosis

Toxoplasma exists in two forms—the free proliferative form, found in acute infection, and the cyst form which is associated with the development of antibodies in the host. In contrast to the free form the cystic form is well tolerated by the host and does not set up an inflammatory reaction. It can remain dormant in the tissues of animals for the period of their natural lives; it has been found in a baby 32 months after congenital infection (Couvreur, 1955) and also at autopsy in men who have died of causes other than toxoplasmosis (Kean and Grocutt, 1947).

Toxoplasma infects many, probably all, species of mammals, including man, and also some species of birds. Nor has it any more respect for the boundaries of geography than for those of zoology, being found in the Arctic Circle and even more commonly in the tropics. Results of serological surveys of its incidence in adult man are shown in Table I.

TABLE I.—SEROLOGICAL EVIDENCE OF TOXOPLASMOSIS IN MAN

Place	No. tested	% +ve*	
U.S.A. Memphis (Tenn.)	987	17	Gibson *et al.* (1956)
U.S.A. Pennsylvania ..	144	35	Feldman and Miller (1956)
U.S.A. Navajo Indians	236	4	Feldman and Miller (1956)
Norway	1,599	7	Harboe (1952)
Iceland	108	11	Feldman and Miller (1956)
Guatemala	100	94	Gibson and Coleman (1958)
New Zealand	258	46	Manning and Reid (1956)
England	1,104	29	Beattie (1957)

*Dye-test titre of 1 : 16 or more except Norway where the titre was 1 : 10.

Noteworthy is the marked difference from place to place. Grönroos (1955) observed considerable variation within a comparatively small area, as did Beverley (1956) who found dye-test antibodies to a titre of 1 : 4 or more in 75% of adults in Spilsby but in less than 35% in Southwell.

On average antibodies were more frequently found in rural (36% at a titre of 1 : 16 or more) than in urban districts (22·5%) (Beverley, 1956). Piekarski (1955) made a similar observation, but Gibson (1956) found no difference.

Serological surveys on animals give a similar picture (Table II) and show even more striking

TABLE II.—SEROLOGICAL EVIDENCE OF TOXOPLASMOSIS IN ANIMALS

	Per cent positive*					
	Cats	Dogs	Swine	Sheep	Cattle	
Tennessee	49	16	21	24	0	Eyles *et al.* (1959), Gibson and Jumper (1960)
Holland	—	—	50	64	21	Roever-Bonnet (1957*b*)
Czecho-slovakia	77	20	8	12	8	Havlik and Hubner (1958)
Sheffield	16	32	12	16	—	Rawal (1959*a*) and unpublished

*Dye-test titre of 1 : 16 or more.

differences. In New York State, Feldman and Miller (1956) found no antibodies in two herds of cattle but 38% and 49% in two others. Among the sheep of the Navajo Indians the incidence was 5%, but in Kentucky sheep 56% (Feldman and Miller, 1956). Beverley (1959) found antibodies in 34% of sheep in two West Riding flocks but in 90% of one East Riding flock.

In spite of the vast amount of infection toxoplasma does relatively little harm. If ability to live on good terms with its host be the criterion of the success of a parasite, then toxoplasma is eminently successful. Sometimes of course it does cause harm, the most tragic manifestations being found in congenital infections. Obviously not all infections, certainly not all human infections, are congenital. If they were the incidence of toxoplasma antibodies would be highest in childhood, for this is an infection which, though present in fœtal life, stimulates antibodies in the baby. In fact the reverse is the case; the incidence of antibodies increases with advancing years.

The commonest manifestation of acquired toxoplasmosis is lymphadenopathy, clinically indistinguishable from infectious mononucleosis, and sometimes giving a similar blood picture. It is never, however, accompanied by a Paul-Bunnell reaction. In England about 7% of cases of "glandular fever" in which there is no Paul-Bunnell reaction are, in fact, cases of toxoplasmosis (Beverley and Beattie, 1958).

Siim (1959) reported on 40 patients with adenitis of unknown origin examined in the outpatient department of the Finsen Institute, Copenhagen. Of these, 5 (13%) had toxoplasmosis. Other causes were Hodgkin's disease (2), metastases (1), reticulum cell sarcoma (1) and tuberculosis (2).

The severity may vary from a few enlarged symptomless glands, found on routine medical examination, to generalized glandular enlargement with marked weakness, muscle pains and protracted convalescence. Toxoplasms have on several occasions been isolated by muscle biopsy. Complete recovery is the rule but a few cases have been complicated by myocarditis and by choroido-retinitis. This has given rise to the suspicion that primary myocarditis might be due to toxoplasmosis. There is at least one proven instance of this (Potts and Williams, 1956) but serological investigation of patients suffering from myocarditis does not suggest that toxoplasmosis is a common cause. The position with regard to choroido-retinitis is obscure. It is estimated, on serological grounds, that in 25% to 35% of cases toxoplasmosis is the cause, but how much is of congenital and how much of acquired origin is unknown. Other reported manifestations of acquired toxoplasmosis have been encephalitis and a fatal typhus-like disease. The former has been rarely, and the latter never, seen in this country.

The next question is whence does infection come? In view of the wide distribution of toxoplasma in the animal kingdom this should be easy to answer. But from the very abundance of infected animals comes difficulty. Thus Gibson and Eyles (1957) in the neighbourhood of a congenitally infected baby found infection in dogs, cats, mice, hens, ducks and pigeons. Only the wild birds were free. They regarded toxoplasmosis as a zoonosis passing between many species of animals including man.

Of man's domestic animals, dogs and cats have been most frequently suspected. It is indeed possible that a susceptible person caring for an acutely sick animal might pick up the infection, but in many cases there is no history of intimate contact and it is hardly likely that casual contact with a latently infected animal would suffice. Moreover Beverley *et al.* (1954) found no difference in the incidence of toxoplasma antibodies in men who kept dogs and in others who did not. There was, however, a significantly higher incidence in veterinary surgeons, abattoir workers and rabbit handlers, particularly rabbit trappers, but Roever-Bonnet (1957*a*) was not able to confirm this in abattoir workers.

It should not be forgotten that the animal with which man is most in contact is man. There is no definite proof of man-to-man transmission, but Kemp (1950) suspected it in a nurse who had cared for a toxoplasmosis patient. Paton *et al.* (1958) thought it might have taken place in the case of two brothers who slept in the same bed, and Jacobsson (1953) found infection in a father and son. Sometimes, moreover, high-titre antibodies, indicating recent infection, are found in the healthy siblings of patients with acquired toxoplasmosis (Beverley and Beattie, 1958). This may indicate man-to-man transmission but may equally well point to infection from a common source. Against the theory of man-to-man transmission is the fact that antibodies are no more frequent in husband and wife than they would be by chance.

Spread of infection must be considered in relation to the two forms of the parasite—the free proliferative form which dies soon after it leaves the body of its host, being particularly

susceptible to drying, and the cyst form which survives for rather longer periods. Toxoplasma is discharged in the secretions and excretions—milk, urine, sputum, saliva, nasal discharge—of infected animals but, as the evidence has been obtained by animal inoculation, the form of the parasite is unknown. Spread of the proliferative form would have to be immediate, by inhalation or by the penetration of skin or mucus membrane; gastric juice destroys it fairly readily, so infection by ingestion is improbable. On the other hand the proliferative form readily infects animals when instilled into the nose. Beverley (1950) succeeded in infecting mice by placing them in a chamber into which toxoplasms of the R.H. strain were sprayed so that each mouse inhaled 5 to 9 parasites. In a somewhat similar experiment Kunert and Schmidtke (1954) succeeded in infecting guinea-pigs but not mice. These, however, were drastic experiments under highly artificial circumstances.

The cyst form withstands external influences better than the proliferative form. In dead animal tissue it may remain alive for at least sixteen days at refrigerator temperature (Bain *et al.*, 1956). Nor is it destroyed by the gastric juice. Experimentally it has been found easy to infect animals with cysts by the oral route, a single cyst being enough to infect a mouse. Animals, and man, might therefore acquire infection by swallowing material contaminated with cysts discharged by infected animals. Unfortunately we do not yet know if cysts are discharged, nor does this seem likely, for highly susceptible mice may be kept in very close association with infected mice for long periods without becoming infected and the same is true of dogs (Jacobs, 1957). Cysts may be found in the lung alveoli of experimental animals (Lainson, 1958), and thus infection spread by cysts in sputum. Against this is the failure of infection to spread from animal to animal in close association.

Cysts are, however, present in the flesh of infected animals and the only known way, apart from congenital infection, by which mice become infected is by cannibalism. Dogs and cats might become infected when hunting, and man by eating meat containing cysts. Very probably this does occur. Siim (1951) reported that one of his toxoplasmic patients had been on a raw meat diet for medical reasons. So had the tuberculous patients with high dye-test titres described by Desmonts (1959). Certainly there are opportunities for infection in this way, for Rawal (1959*a*) isolated toxoplasma from the brains of 6 of 100 sheep and Jacobs (1957) from the diaphragms of 12 out of 50 pigs.

For meat to produce infection it must be eaten raw or very imperfectly cooked; Rawal (1959*b*) found the incidence of toxoplasma antibodies to be the same in meat eaters (Christians and Moslems) as in vegetarians (Hindus) in Bombay.

In this country there is little consumption of uncooked meat. The little there is has occasionally given rise to trichinosis, which has been found predominately in women, particularly young women, who hurriedly put together a sandwich before going to work. The man of the house, who insists on having his meat properly cooked, escapes. If, therefore, toxoplasma infection came from eating infected meat it would be commoner in women than in men, and that is not so.

Another suggested mode of transmission has been by blood-sucking insects, but no one has yet succeeded in effecting this experimentally.

In some respects analogous to toxoplasmosis are coccidiomycosis and histoplasmosis which, in certain areas, are widespread but cause relatively little disease. These we believe are spread by the inhalation of spores from the soil. Toxoplasma, however, is such a strictly intracellular parasite that it is almost inconceivable that it could survive, let alone multiply, in soil.

The puzzle is somewhat like that of Q fever in which inhalation appears to play a prominent part but the consumption of infected milk has also been incriminated. Toxoplasma may be found in milk, though with what frequency is unknown. Pasteurization temperatures, however, destroy it (Rawal, 1959*c*), but some unpasteurized milk is still drunk in this country. Milk, if it be a source of infection, cannot be the only one for the inhabitants of Bombay boil their milk yet have toxoplasma antibodies as frequently as the inhabitants of Sheffield.

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Dr. J. K. A. Beverley (Sheffield):

Congenital Toxoplasma Infections

Infection with *Toxoplasma gondii* in human beings usually remains subclinical; even so, before immunity becomes established, some degree of spread occurs in the body by direct extension from the portal of entry, by the lymphatics, by the blood stream, or by combinations of these methods. When spread occurs by the blood stream, minute secondary foci may be established in any of many tissues. If a primary infection occurs in a pregnant woman, secondary foci may develop in the placenta and these may release toxoplasma into the fœtal circulation; so, the seeds of congenital toxoplasmosis are sown.

What happens next depends on several factors —the age of the fœtus, the size of the infecting dose and the virulence of the strain of toxoplasma. At best, the infection may be overcome without any permanent damage; this does happen for we know of one patient with bilateral choroiditis whose twin had no signs at all and yet was found to have high antibody levels when aged 2 years. At worst, a generalized infection develops and leads to fœtal death.

Infection in early pregnancy may lead to abortion (Magnusson, 1951; Wildführ, 1954) but it is not a common cause of this for Feldman and Eichenwald (1953) investigated 95 cases without finding any evidence of active toxoplasmosis. Depending on the exact time infection later in pregnancy may cause a miscarriage, a premature live birth, a stillbirth at term, or a live birth with stigmata. If fœtal infection occurs shortly before birth, the child may be born alive and appear quite normal only to develop changes during the first three months of post-natal life.

The fœtus does not make its own antibody. It is dependent on antibody acquired passively from its mother. This antibody in the presence of "activator"—a complement-like component of serum—is toxoplasmocidal. The concentration of the passively acquired antibody in the fœtal plasma depends on the permeability of the placenta to maternal antibody. Before the 32nd week of pregnancy, practically no antibody crosses to the fœtus, but during the next month gradually increasing quantities, and in the last month large amounts, are transferred. The fœtal concentration is also proportional to the maternal concentration and at term the ratio on the average is 5 : 3. The maternal antibody concentration in its turn is in some measure related to the permeability of the placenta in the reverse direction for this governs the amount of antigen transferred back from fœtus to mother.

Early in intra-uterine life, the fœtus has no complement or activator and it is not until the early days of post-natal life that all the components of a fully hæmolytic complement are present. In general the antibody and complement concentrations in the fœtal plasma are greater, the longer the duration of the pregnancy. The effectiveness of passively acquired antibody is greatest in the fœtal body fluids and very much less in the cells—where most of the parasites are. There is evidence that the greater the similarity of maternal and fœtal antigens, such as A B O and other blood group antigens, the greater is the penetration of the passively acquired antibody into the fœtal cell membranes.

With the first shower of toxoplasms from the placenta into the fœtal circulation, a parasitæmia is established. Some of the organisms are engulfed by reticulo-endothelial cells and settle in such tissues as liver or spleen to multiply there and spread locally with the formation of focal lesions which may undergo central necrosis. Generally speaking, the more actively growing the tissue is, the more likely it is to be the site of toxoplasma proliferation. Hepatosplenomegaly with or without jaundice is a common finding. Disturbances of the hæmopoietic system may occur and we have been concerned with two cases where congenital purpura was the only clinical finding. Some cases simulate hæmolytic disease of the newborn (Bain *et al.*, 1956). At this visceral stage of the infection, lymph-node enlargements, generalized œdema and skin rashes (usually morbilliform) may occur.

Usually the fœtus or infant survives this stage and the systemic effects gradually subside; central nervous system involvement may follow, probably because the defence mechanisms operate less efficiently here. By far the commonest site of clinical manifestations is the choroid of the eye. The size, the situation in the choroid and the

number of the lesions vary enormously. Sometimes spread occurs to other tissues of the eye causing a panophthalmitis and a useless microphthalmic eye may result. If confined to the choroid and retina, an extensive lesion will cause a white "reflex" on shining a light into the eye and such a defect is usually noticed at a very early age. A less extensive lesion, but one involving the macula, may be the underlying cause of a searching nystagmus or a squint, first noticed about the time that binocular vision should be established. Lesions just off the macula may not be found until early school life when the child is first suspected of having a visual defect and an ophthalmoscopic examination is made. Other lesions in the periphery of the fundus may not be found until much later in life when an acute exacerbation occurs, accompanied by vitreous haze and diminution of visual acuity. Some lesions are found on routine ophthalmoscopy and have never given rise to symptoms.

Toxoplasmic choroido-retinitis is by no means a rarity. Over a nine-year period (July 1950 to June 1959) 89 patients who had both choroido-retinitis and toxoplasma antibodies were seen at the United Sheffield Hospitals and 20 such cases were seen at the Barnsley Beckett Hospital (Table I). The population of the catchment areas of the

TABLE I.—AGE DISTRIBUTION OF PATIENTS WITH CHOROIDO-RETINITIS SEEN AT THE UNITED SHEFFIELD AND BARNSLEY BECKETT HOSPITALS 1950–59

Decade ..	..	1	2	3	4	5	6	7	Total
No. of cases	..	15	22	26	20	15	7	4	109

Sheffield Hospitals is 675,360 and that for Barnsley 169,180. While we feel confident of the diagnosis for those patients in the first decade, and for most of those in the second decade, we are not so certain of many of the remainder for, even though the clinical appearances were the same as those of the younger patients, their antibody titre was much lower, in some cases it was as low as the levels commonly found in normal adults. This is only to be expected, for antibody titres fall with the passage of time since infection (Table II).

TABLE II.—DYE TEST TITRES OF YOUNG PATIENTS WITH CHOROIDO-RETINITIS

Age (years)	No. of cases	Average	Range
At birth	2	1 : 3,750	1 : 5,700–1 : 1,800
<1	8	1 : 850	1 : 2,000–1 : 100
1–5	12	1 : 374	1 : 1,000–1 : 46
6–10	12	1 : 125	1 : 860–1 : 15
11–15	11	1 : 51	1 : 160–1 : 10
16–20	11	1 : 30	1 : 98–1 : 10

While there must have been variations in the age of onset of symptoms and also while it must be realized that some of these patients were known to have choroido-retinitis many years ago—before the possibility of a toxoplasmic ætiology was appreciated—the incidence in the different 10-year age-groups does not appear to increase with age; this supports the contention that most cases are the result of congenital infection.

The brain and spinal cord are liable to damage. A common site is the layer of tissue a few mm external to the ependyma of the lateral ventricles, but more superficial parts of the cortex, the basal ganglia, the medulla and the cord may also be affected. The cerebellum, by contrast, is rarely involved. The lesions are focal but may be so numerous as to become confluent. If this happens in the sub-ependymal areas, portions of tissue may be shed into the ventricles and start an ependymitis, involve the choroid plexuses and lead on to meningitis. Should larger portions of tissue be detached, blocking of the aqueduct and consequent obstructive internal hydrocephalus may occur. Sometimes, usually in intra-uterine life, there is such extensive loss of cortical tissue that microcephaly with internal hydrocephalus results.

Calcification occurs in the brain lesions, more particularly in the healing stages, and thus may be absent at birth but present a few months later. It is often detectable on X-raying the skull and usually takes the form of curvilinear streaks in line with the walls of the lateral ventricles. Large opacities of irregular outline may be found when more superficial parts of the cortex or the basal ganglia are involved.

Because damage can occur in almost any part of the brain, the neurological signs vary enormously. Some children are of normal intelligence while others are virtually decerebrate animals. Convulsions during the active process are quite common; a few cases develop epilepsy later—presumably as a result of the "healing" processes of cicatrization and calcification. Hypothermia may be present if the basal ganglia are involved. Palsies and sensory changes may be found if the child survives to an age when tests can be made.

In most cases of congenital infection, irreparable damage has already been done. In the older patients the lesions are usually inactive though the infection may still be present but dormant. Acute exacerbations of choroido-retinitis may occur, particularly in early adulthood. In the neonatal period, however, there is usually some residual activity and "healing" is not yet complete. For these cases and for those adults experiencing exacerbations treatment should be attempted. Toxoplasma are sensitive to Pyrimethamine (an anti-folic-acid agent) and to the sulphonamides (anti-paraminobenzoic-acid agents) which inhibit multiplication. Neither drug alone will eliminate infection, but when given together there is a synergy and the combination will eliminate proliferative forms of the parasite. The cysts are more resistant but, in experimental mice, even they will succumb to

prolonged treatment. Though the cysts themselves do not cause damage they are reservoirs of potential agents for future recrudescences. Consequently serious consideration should be given to the prolongation of treatment for several months after the acute stages of the infection have been controlled. These drugs are toxic and a careful watch must be kept on the patient's blood for signs of folic-acid deficiency. Toxoplasma induce both humoral and tissue antibodies, and so give rise to a hypersensitive state. The tissue reactions tend therefore to be granulomatous but they can be controlled or minimized by the concurrent administration of corticosteroids. The specific anti-toxoplasma therapy should, however, be continued for at least a fortnight, preferably longer, after the cessation of the cortisone therapy.

Congenital toxoplasma infection occurs in animals other than man. Among the usual laboratory animals we have, so far, found it in three strains of mice—Swiss, Albino and Astrex—and in multimammate rats and rabbits. The maternal infection need not take place during pregnancy, and once established fœtal infection may occur in several subsequent pregnancies, being found in the fifth pregnancy in Swiss mice and multimammate rats. Most of the work so far has been done with Swiss mice and on the average almost half the litter was infected, sometimes only one mouse, sometimes all of them; there was also a higher neonatal mortality than in controls. Congenitally infected Swiss mice themselves usually deliver infected offspring without infection from an external source and, up to the present time, such transmission has proceeded as far as the sixth generation. We have no information yet on this point in the other species.

So far these findings might, in part, be explained on the grounds that women and all the animal species already mentioned have a placental barrier only one or two cell layers thick, hence transplacental passage would be easy. But congenital transmission also occurs in sheep which have a syndesmo-chorial placenta—five layers thick. In the spring of this year we (Beverley and Watson, 1959) isolated toxoplasma from the aborted or still-born lambs of 6 of 39 aborting ewes in Yorkshire. Infection in a ewe does not necessarily kill the lamb for one ewe had twins, one born alive and the other dead and from its brain we isolated toxoplasma.

I have mentioned animals for two special reasons. One is that further study on these lines may help to explain the frequency of infection in many species of domesticated and semi-domesticated animals, and the variations in the incidence of infection found in different geographical areas. The second is to have another opportunity of emphasizing that findings in animals should be applied to humans only with great caution.

From May 1952 to April 1953, through the courtesy of Dr. C. C. Bowley, the director of the Sheffield Regional Transfusion Centre, toxoplasma serum antibody levels have been studied in 298 Rh-negative women through their pregnancies. Early in pregnancy 115 (38·5%) of these had low dye-test antibody levels and the remainder were negative. Of the 183 who were negative, only one became positive (to a titre of 1 : 32); by the time we had traced her, she had aborted and unfortunately the products of abortion had been discarded. None of those who were positive in early pregnancy had any subsequent alteration of antibody level to indicate active infection. From this there seems no justification for terminating pregnancy on the grounds that a woman has dye-test antibodies, and indeed, such antibodies make active reinfection unlikely. The only case in which therapeutic abortion might perhaps be considered is when, during pregnancy, the woman's antibody level rises from zero to a high titre. Even then, it must be borne in mind that the child need not necessarily have an infection with gross damage.

Ten years ago, one was cautious in answering the question nearly always asked by parents of a congenitally infected child—"If we have another child, will it be all right?" Since that time many women have had a pregnancy subsequent to the one when they had an infected child. Both in this country and the U.S.A. these pregnancies have been followed very carefully and, so far, not one of them has resulted in another congenital infection. One woman we know has had three subsequent normal children. Another woman, herself a case of toxoplasmic choroido-retinitis probably congenital in origin, had an acute exacerbation of her choroiditis with marked rise of serum antibody levels while she was pregnant. Her child was quite normal. Thus a reasonable assurance can be given to parents that the same thing will not happen again.

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Laboratory Diagnosis of Toxoplasmosis

Although toxoplasmosis may sometimes present a rather characteristic clinical picture, diagnosis can only be made with the aid of the laboratory, which may assist, apart from exclud-

ing other diagnoses, by attempting to isolate the parasite, studying biopsy material, examining for serum antibodies, and determining skin sensitivity to toxoplasma antigen.

Isolation of the parasite is the only completely satisfactory method of demonstrating infection. This has been done from most tissues of the body, particularly the lymph nodes, blood, C.S.F., brain and muscle; and in the rarer cases where antibody formation is delayed or feeble, or the patient is in a very early stage of the disease, isolation may be the only method of making a diagnosis. For example, toxoplasma has been isolated from the blood four days after the onset of an infection acquired in a laboratory (Kayhoe *et al.*, 1957), and from the amniotic fluid of a baby with anencephaly and from the C.S.F. of a baby with hydrocephalus, in both of whom serum antibodies were absent (Schmidtke, 1957). The parasite has also been isolated from the blood of a healthy woman in charge of a dog ill with toxoplasmosis (Prior *et al.*, 1953).

The technique consists essentially of the inoculation of body fluids or ground-up tissues intracerebrally or intraperitoneally into mice from toxoplasma-free stock. This may produce acute infection in the mice in a few days. More often blind passage is needed before infection can be demonstrated, but according to Wildführ (1954) no further isolations are to be expected after the third passage. Even where parasites may be impossible to demonstrate in the inoculated mice the presence of latent infection may be shown by the occurrence of dye test antibodies in the mice several weeks after inoculation (Desmonts and Le Tan Vinh, 1957). Instead of mice, guinea-pigs or hamsters may be used, and positive results have also been obtained by inoculating tissue cultures and chick embryos (Jacobs, Fair and Bickerton, 1954). Unfortunately even in cases that on good clinical and serological grounds can be regarded as due to toxoplasma it often proves impossible to isolate the parasite, and when isolated it may only be after considerable delay and labour.

Gland biopsy. When the patient has lymphadenopathy, and other laboratory examinations have left the diagnosis in doubt, it may be necessary to remove a gland for histological examination. Some of the ground-up gland may also be used for isolation experiments.

The characteristic appearances found correspond to Robb-Smith's description (1947) of lympho-histocytic medullary reticulosis. This consists of a reactive hyperplasia of the lymph-node tissues with small collections of cells of a particular type scattered through the medulla. These cells are rather large mono- or multinucleate epithelioid cells with a finely granular eosinophil cytoplasm. These appearances were encountered in 23 biopsies examined by Saxén and his colleagues (1958) and in each case serological tests afterwards supported their toxoplasmic ætiology. It seems probable, however, that in a number of cases, especially in the earlier stages of the condition, the appearances will be less distinctive and will show little more than a non-specific reactive hyperplasia.

It is very difficult to find the parasites in sections of suspected glands and most workers report negative results. Stanton and Pinkerton (1953) by serial sectioning were able to find two cysts, each lying in a sinus with no particular reaction around it. Cysts are relatively easy to see in section but it seems probable that scanty extracellular parasites, with standard methods of fixation and staining, even if present, are virtually unrecognizable. Improved histological techniques may assist in finding parasites. Wilder (1952) recommended mounting tissues in celloidin, and Armstrong and Fulton (1959) have found an acridine orange fluorescent technique useful for showing up scanty parasites.

Serology. Testing for serum antibodies is the most useful and practical laboratory aid in diagnosis and the one in most general use. Two tests are available—the Sabin-Feldman dye test (Sabin and Feldman, 1948) and the complement-fixation (C.F.) test of Warren and Russ (1948) as modified by Sabin (1949). The dye test is the more sensitive indicator of the presence of toxoplasma antibody but has the disadvantage of being technically more exacting, requiring the maintenance of a standard strain of toxoplasma in the laboratory by frequent passage through mice, the use of a suitable peritoneal exudate from an infected mouse within an hour of its withdrawal, and of a human serum free from antibody and containing an adequate amount of thermolabile "accessory factor". Only about 10% of human sera are suitable for this purpose. When the parasites are incubated with a serum containing antibody and with the "accessory factor" serum they lose their ability to stain with alkaline methylene-blue, the end-point of a serum being the dilution at which 50% of the parasites are still unstained. In spite of the difficulties of the test Rubin (1958) found that his laboratory did not show a variation in titre of more than one tube in repeated tests on sera, and different experienced laboratories have found that when testing the same sera they do not usually get significantly different titres (Sabin *et al.*, 1952). The complement-fixation test on the other hand is a straightforward test, using as antigen an extract of the toxoplasma-infected chorio-allantoic membrane of the chick embryo, previously subjected to high speed centrifugation

to eliminate non-specific reactions. This antigen can be maintained in the frozen state for months.

The interpretation of the dye-test results is made difficult by the frequent occurrence of low-titre antibodies in the normal adult population. After any passive antibodies acquired from the mother have been lost, the sera of normal young children give uniformly negative results, but with increasing age the incidence of positive sera rises, the rate at which it rises and its final level in the adult varying with the community. For example, Beattie (1957) found in England 36% of country dwellers and 22% of town dwellers giving titres of 1/16 or over. Feldman and Miller (1956) found a rather similar incidence in the United States. In the age group 30–39 years, the percentage positive at 1/16 or more ranged from 26% to 45% according to locality. On the other hand this age group had an incidence of 78% in the Honduras and 77% in Tahiti. The majority of these positive sera, however, were of low titre. Only 0·2% of Beattie's rural population and 0·17% of his urban population had a titre of 1/256. The significance of a positive dye-test result must be considered against this background. It is evident that a titre of 1/256 can reasonably be regarded as suggestive of a recent toxoplasma infection and in fact, in many cases of frank generalized infection, the titres will run at a much higher level. However, as sera may be persistently strongly positive at a fairly steady level for long periods the most satisfactory evidence of a recent infection is the demonstration, by repeated serum testing, of at least a fourfold change in titre and preferably an eightfold change (Sabin *et al.*, 1952). Where low titres are obtained it is impossible to relate them to a present illness by a single test and here repeated testing at intervals of several weeks is essential.

Commonly in an acute generalized infection the dye test becomes positive in less than two weeks and rapidly rises to a high titre of 1/256–1/4,000 or more. This then falls over a period of months and persists at a relatively low level for years. In individual cases great variation in the type of response may occur. There may be a delay of over a month before the serum becomes positive, although it may finally reach a high titre, or the highest titre reached may not be much above levels found commonly in the population. A high titre in itself is very suggestive of a recent infection but this has sometimes been found in healthy persons, particularly in home contacts of known cases, e.g. Beverley and Beattie (1958) report a child of 3 with toxoplasmic lymphadenopathy who had two brothers without a history of symptoms but with titres of 1/1,600 and 1/5,000. A high titre may coincide with an unrelated illness. Huldt (1958), for example, reported 2 cases of lymphadenopathy with strongly positive dye-test titres in which biopsy of the lymph nodes showed lymphatic leukæmia in one and tuberculosis in the other, and Sabin (1956) reports the case of a man convalescing from a proved histoplasma pneumonitis developing a high titre of dye-test and complement-fixing antibodies.

In congenital toxoplasmosis a high dye-test titre is normally found in mother and child at birth, but it is impossible to distinguish at birth between a high titre in the infant due to passive transfer and one due to active infection. If due solely to passive transfer the antibody level will have shown a marked fall by the end of four months and will be absent or negligible before the end of the first year. In active congenital infection the titre is maintained and slowly falls over the following few years. It is doubtful if it ever disappears. Cases of latent or undiscovered congenital toxoplasmosis must occur, for positive sera may be found unexpectedly in small children without clinical toxoplasmosis; for example, Paul (1954) refers to two children aged 14 months and 18 months suffering from vaccinial and pertussis encephalitis, both with dye-test titres of 1/64, both their mothers having high-titre sera.

Complement-fixing antibodies are demonstrable much less commonly in the normal population. Macdonald (1950) found 5% of normal adults with a titre of 1/10 or more, and other workers in this country have found a similar or lower incidence (Cathie and Dudgeon, 1949; Beverley *et al.*, 1954). In an acute infection complement-fixing antibodies appear later than dye-test antibodies, the titre attained is lower and it falls earlier. Their presence therefore tends to suggest that an infection is well established and may still be active. Owing to their relative rarity in the normal population they should be given more significance than a positive dye test combined with a negative C.F. test. Although the C.F. titres in an infection may roughly parallel the dye-test titres there are sufficient exceptions to this to suggest that the tests are detecting different antibodies.

In congenital toxoplasmosis, at birth both mother and child normally give a high titre in the C.F. test but Sabin and his fellow workers (1952) report the occurrence of babies with congenital toxoplasmosis negative by C.F. test although their mothers' sera were positive. They regard this as a sign that the child has an active infection. The titre in the baby gradually falls over the following few years and eventually disappears, although Eichenwald (1956) found that by the age of 5 years 44 out of 60 children with congenital infection were still giving positive results.

Toxoplasmic choroido-retinitis is the most

difficult of the recognized manifestations of toxoplasma infection to diagnose serologically. The dye-test antibodies found are usually of a level commonly found in the normal population, for example in 21 cases proved histologically only three gave titres of over 1/64 (Jacobs, Cook and Wilder, 1954). However, low-titre antibodies are distinctly commoner than in normal persons in cases of choroiditis, especially those of a granulomatous type and in which other causes have as far as possible been excluded (Woods *et al.*, 1954). In the individual case a low-titre dye test cannot be regarded as diagnostic. The result must be weighed up with other clinical and laboratory findings. Repeated serological testing may demonstrate marked changes in titre (Perkins, 1958) but in many cases of probable toxoplasmic choroiditis significant changes do not occur. In children, however, owing to the rarity of antibodies in normal children, a positive dye test can more confidently be related to a choroiditis. The positive dye test is accompanied in a proportion of cases by a positive C.F. test and we regard this as increasing the possibility that the eye condition is due to toxoplasma infection and as indicating that the infection is probably either active or has recently been active. Negative serology in an eye infection is of course good evidence against a toxoplasma infection.

Although the complement-fixation test and the dye test are at present the only serological tests carried out regularly in the diagnosis of toxoplasmosis, Jacobs and Lunde (1957) have devised a hæmagglutination test using tanned red cells sensitized with toxoplasma antigen. This test also has technical difficulties but there is hope that it may prove more satisfactory than the dye test. Lunde and Jacobs (1958) have carried out a survey comparing these two tests and have found the results paralleling one another closely. Further observations on this test are needed.

Skin testing. Frenkel (1948) showed that persons infected with toxoplasma developed skin sensitivity to toxoplasma antigen. This appears to be a specific reaction and is practically always associated with a positive dye test. However, patients with a positive dye test may have a negative skin test, and there is no correlation between the strengths of the two tests. The skin test is useless in children under 2 years and gives a negative result in the early stage of an acute infection. Nevertheless the test may be valuable as a screening test when it is not practicable to do serological testing and, because large numbers of persons can be rapidly examined, for carrying out epidemiological surveys.

Although laboratory tests may sometimes establish the diagnosis beyond doubt, we are left with a number of cases in which the tests are only suggestive and others, especially eye cases, in which a positive result leaves the diagnosis only a possibility but in which a negative result tends to exclude. At present the greatest needs on the diagnostic side are for simpler and more reliable methods of demonstrating the parasite, for a serological test as sensitive as the dye test but less exacting, and for a reliable method, apart from demonstrating changing titres, for distinguishing active disease from old or burnt-out infection.

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Meeting
October 23, 1959

Observations on Social Conditions, Fertility and Family Survival in the Past [*Résumé*]

PRESIDENT'S ADDRESS

By H. J. MALKIN, F.R.C.O.G.

Nottingham

THROUGH the past centuries, social conditions have improved gradually. Education has increased, medicine shown advances, and the expectation of life lengthened considerably. Whatever the conditions of the times, however, reproduction has gone on and families have been founded. My observations are on *this* country, and as it is likely that royal families throughout the centuries received the best care, attention, and social amenities available, I should like to concentrate mainly on them, and see how they fared through the years.

I propose to exclude the present century, and some of the last, as the application of scientific knowledge to medicine, and to everyday life, has been so rapid and spectacular in the last hundred years or so, that the subject would be inexhaustible. It is, however, necessary to mention that the last century brought us antisepsis, asepsis and anæsthetics. For the measure of popularity this last received, we owe a good deal to Queen Victoria. Anæsthesia had been condemned for use in childbirth, as being unnatural and unnecessary, and in fact, quite amoral. The Queen's agreement to its use during her own confinements was, therefore, of great assistance to the obstetricians, as well as to the surgeons, who were so anxious to see anæsthesia used universally and without prejudice, when and where necessary.

TABLE I.—HANOVERIANS

Monarchs and their consorts	Pregnancies and children	Survivors to adult life
George I and Sophia	2 children	2
George II and Caroline	9 children	7
George III and Charlotte	15 children	13
George IV and Caroline	1 child	1
William IV and Adelaide	1 premature 1 premature stillbirth 1 abortion	0

Hanoverians (Table I)

George I and his wife had only 2 children, partly from lack of opportunity, as the Queen had been virtually imprisoned since the children were very young. This George, who cared little for England, came with no Queen, but his 2 mistresses.

His son and successor had married Caroline of Anspach. They had 9 children—2 died in infancy, and 7 survived their mother. In spite of this Queen's devotion to learning, and attention to her husband and children, the Household must have been a strange one to live in. The parents disliked their eldest son, and doted on a younger, the eldest son returned his parents' dislike, and amongst the brothers and sisters there was little affection but a good deal of detestation and jealousy. The Queen, who had always taken a great interest in progress, heard of some successful inoculation against smallpox in Constantinople, and after satisfying herself that 6 condemned criminals had been inoculated successfully in this country, she allowed 2 of the princesses to be treated similarly. A courageous move perhaps, but she was certainly a realist. On her deathbed, she begged the King to grant her wish and marry again. The King, scarcely able to speak for tears and sobs, murmured that he could *never* do that, then, after a pause added that he thought "perhaps a mistress or two instead". The Queen smiled and said "Mon Dieu, the one doesn't prevent the other"! At George II's death, his son Frederick Prince of Wales should have been king, but he died before his time. Known in the lampoons of the day as "Poor Fred", he was generally unpopular, though a great sponsor of the arts. He was obstinate and thoughtless, as is shown by his determination not to accede to his parents' request that their grandchild should be born at Hampton Court, where they were all in residence at the time it was due. As soon as his wife's labour had begun, Frederick called his coach, and into it bundled the Princess of Wales, a Lady-in-Waiting, 2 female attendants, a versatile member of the Household who was Valet-de-

Chambre-Surgeon-Accoucheur, the Dancing Master, and several others. They drove furiously to St. James's Palace, where nothing was ready, and a couple of tablecloths had to be found, aired, and used as sheets for the confinement which in due course took place. The 8 confinements which followed this were rather less spectacular, but family life here again lacked harmony, and the majority of the children married unhappily or unsatisfactorily. The eldest son, George, did not, however; he married Charlotte of Mecklenburg-Strelitz in 1761, and by the twenty-first year of their marriage they were the parents of 15 children. Although 13 of them lived to adult life, they were not nearly as successful as their parents had been in leaving legitimate descendants behind them. Of the married daughters, none had children, and of the unmarried ones 2 had children. The 7 surviving sons all married. The 4 youngest between them had 7 children, including the Duke of Kent's daughter, Victoria. The 3 eldest had less success. The Prince Regent, afterwards George IV, had one daughter by his wife Caroline, the Princess Charlotte, and the story of her early death in childbirth has been ably told by Sir Eardley Holland (1951) in his paper "The Triple Tragedy". Triple tragedy it certainly was in the death of first baby, then mother, then doctor, but not for England's future. This stillborn baby had, it is true, a father with the Coburg stability, but it could scarcely have had 2 more unstable grandparents than the moody and emotional Prince Regent, and his wife Caroline, whose "unusualness" turned to eccentricity, and later to a form of madness. Certainly there had been much in her marriage to make her crazy, but the tendency was there, and came to the surface too easily. It would have been a sad alternative for this country to have had Charlotte or Charlotte's child as monarch instead of Queen Victoria. The next son of George III having died childless, it fell to the lot of the third son to succeed to the throne as William IV and to produce the necessary heirs. Unfortunately his wife, Adelaide, had a most disappointing obstetric history. She had a premature baby which died the same day, a miscarriage, and a six-weeks-premature child which lived for three months when it died in a convulsive fit. So again there was no direct heir of the reigning king, and on his death, his niece, Victoria, became our Queen. The rather eccentric old William IV and his queen had had the welfare of their people at heart, and it was during their short reign that Hyde Park, and other royal parklands, were opened to the public. The previous Hanoverian couples and their families, however, although between them they had produced a large quantity of children, seemed to be found wanting. There was so little loyalty and harmony in the family circle, and so much petty jealousy, that it is not surprising that they did not present an ideal example to their subjects. The first George and the fourth were distinctly unpopular. The first one's wife never came to England; the fourth's was encouraged to stay out of it. The families of the second and third Georges were satisfactory in quantity, but not altogether in quality, and with a few exceptions were conspicuous for being self-centred, self-indulgent, and quite lacking in self-discipline. Although the question of obstetrics did come to the fore in the case of the Princess Charlotte and Queen Adelaide, perhaps the specialty which would have been of the greatest assistance to our Hanoverian Royal Families might have been the psychiatric one.

TABLE II.—STUARTS

Monarchs and their consorts	Pregnancies and children	Survivors to approx. 16 years and over
James I and Anne	7 children 1 premature stillbirth	3
Charles I and Henrietta Maria . .	8 children	6
Charles II and Catherine	1 abortion	0
James II and Anne Hyde	8 children	2
James II and Mary of Modena . .	7 children	2
William and Mary	0	0
Anne and Prince George	4 children 3 stillbirths	0 0

Stuarts (Table II)

A hundred and eleven years before these Hanoverians came to sit on the throne of England, their ancestor, James VI of Scotland, had just arrived in this country to rule as James I. His father being dead, and his mother imprisoned for years, he had been brought up in Stirling Castle by the Earl of Mar, and he seems to have started life badly. His nurse was a drunkard, and fed him on "vitiated" milk. He probably had rickets. Certainly he never walked until he was 5 years old. Strangely enough his wife, Anne of Denmark, though she had a most excellent mother, never walked until she was 9 years old, but was always carried out in the arms of an attendant. In her case, once she learnt to walk she became perfectly normal, and famous for her agility and skill in dancing. Undoubtedly the mediæval custom of binding infants, with their legs straight, and their arms strapped to their sides, must have been responsible for a good deal of damage in those days, and it is a custom which still prevailed in certain parts of this country until the beginning of the eighteenth century. King James and his Queen had 8

children. One died aged 18 of an intermittent fever, probably tuberculosis, 2 children died in early childhood, 2 in infancy, and 1 was premature and stillborn. Only 1 daughter, and 1 son, Charles, lived to a reasonable age.

Charles I and Henrietta Maria also had 8 children, but were a little more successful in keeping them, for a time at least. One died the day of its birth, another aged 4, and 2 more before they were out of their 'teens, of either measles or smallpox. Of the 2 remaining sons, only James left behind him legitimate claimants to the throne. The elder son Charles had married Catherine of Braganza. She had no children, but at least 1 miscarriage, following which she almost died of a fever. She had a sore throat, some sort of rash, described as "spotted", and a very fast pulse. Between sleeping, she gargled, and this, we hope, did rather more good than the live pigeons cut in half and strapped to the soles of her feet to "draw out the poison". She was light-headed for days, and the fever left her extremely deaf. One might assume, I think, that she had a streptococcal septicæmia.

As Charles had left no heir the crown passed to his brother James, who had already been married for the second time. His first wife reared only 2 of her 8 children, and his second wife, Mary of Modena, also had considerable difficulty in bringing up her family. The first child died at 9 months, the second lived until she was 5, the third died in infancy from smallpox, and the fourth only lived for 8 weeks. Then James, afterwards the Pretender, was born. As the Queen had breast-fed her previous children, it was felt that it would be wise to feed this one by hand, and a diet of barley flour, water and sugar, with a few currants added, was chosen. The violent indigestion, colic, vomiting and convulsions which followed never struck anyone as having anything whatever to do with feeding, and it was some weeks later that the Queen herself decided that the diet was at fault, and a wet-nurse must be found. Two further pregnancies, one of the children surviving to adolescence, ends the story of this Queen's efforts at raising a family—7 children, and only 2 alive.

The next monarch, Mary, James's daughter by his first wife, married, but had no children. She and her husband were joint rulers, so after her death he ruled alone, and at his death, James's younger daughter Anne became Queen Regnant. Anne had for a long time been married to Prince George of Denmark, and had not had very happy results as far as founding a family was concerned. She had three stillborn children, then a son who was a hydrocephalic and lived to the age of 11, when he died of scarlet fever, then 3 more children all of whom died within a few hours of their births. So Queen Anne, though she left a name marking an era greatly loved by people interested in architecture, furniture and the acquisition of works of art, left no heir. The Stuarts seem to have had a great deal of difficulty in rearing their not inconsiderable families. Although we know that tuberculosis was constantly about, that scarlet fever and measles were epidemic, that smallpox was a scourge of the times, and that in the seventeenth century, the terrible outbreak of bubonic plague swept over the country with disastrous results, these were by no means responsible for the constant repetition of live births of children who never reached adolescence. There had been the odd miscarriage, but out of the 38 children born to the 4 Stuart monarchs who had any family at all, only 10 survived to adult life. Only 4 had been stillborn, 3 had died of infectious diseases at 18 years of age and just under, but 21 out of the 38 had died in infancy or childhood. These children were all potential heirs to the throne of England, and every care and attention possible would have been lavished on them—perhaps too much. In any case, mortality was startlingly high, and although a public health authority might have been interested in the infectious diseases, I am still struck by the pædiatric angle here, and why, in this particular line of the House of Stuart, the survival rate was so poor.

TABLE III.—TUDORS

Monarchs and their consorts	Pregnancies and children	Survivors to adult life
Henry VII and Elizabeth of York (died of puerperal fever)	7 children	4
Henry VIII and Catherine of Aragon	2 children 2 stillbirths 2 premature stillbirths	1
Henry VIII and Anne Boleyn	1 child 3 abortions	1
Henry VIII and Jane Seymour (died of puerperal fever)	1 (possible Cæsarean section)	1
Henry VIII and Anne of Cleves	0	0
Henry VIII and Catherine Howard	0	0
Henry VIII and Catherine Parr	0	0
Mary I and Philip of Spain	0 (phantom pregnancies)	0
Elizabeth I—never married		

Tudors (Table III)

Not very much more than a hundred years before James VI of Scotland had become James I of England, the Wars of the Roses had ended, and Henry Tudor had become Henry VII. He and his wife, Elizabeth of York, had 7 children. The eldest, Arthur, married Catherine of Aragon, and after his early death the young widow was betrothed to the second son Henry. One

daughter was married to the King of Scotland, and another to the King of France. Three other children had died in infancy, and the Queen died of puerperal fever, nine days after her last confinement. When the King himself died, his son Henry VIII reigned. Henry VIII, as we all know, had 6 wives, his first being Catherine of Aragon. A year after she was married to Henry she had a premature stillborn daughter, and the following year a son who died at 7½ weeks. Two years later she had a third child, stillborn, and the next year yet another, but premature, stillbirth. Another year passed before she produced her only child to survive, the Princess Mary, and 1 more stillbirth followed. Six children of whom only 1 survived. Catherine was able and intelligent, and one of the great victories over the Scots was won under her administration in her husband's absence. All the same, she had not produced a living prince, and the story of her divorce is too well known to mention here. Certain it is that Henry did not let grass grow under his feet on the question of begetting himself an heir. He married Anne Boleyn as his second Queen in January 1533, and in the September of that year, after we understand a "very dangerous travail", the Princess Elizabeth was born. Anne Boleyn fared no better than her predecessor, and apart from the one daughter, had, in three successive years, 3 miscarriages. Her execution was four months after the last of these, and again Henry wasted no time. He married Jane Seymour almost immediately, and after a good deal of anxiety on his part, and presumably on the part of his Queen too, she was delivered on October 12, 1537, of a son, afterwards Edward VI. We know that her labour was difficult, and Henry's reputed remark about saving the child as he could always find another wife may or may not be true, but it is believed likely that she was delivered by Cæsarean section by Dr. Owen, a one-time President of the Royal College of Physicians. What we do know is that she had to conform to the traditional lying-in before her confinement (she retired a month before) and that whatever she had gone through during labour, she had to be present at the christening. This was at night, three days after delivery. A large procession which was preceded, and followed, by quantities of trumpeters, formed up in her bedroom, and she was carried along on a state pallet to the ceremony, which lasted for nearly three hours. Next day she felt indisposed. The next, she was seriously ill, and her death occurred on the twelfth day following her confinement, and quite certainly from puerperal fever. Henry's three further ventures into matrimony ended in Anne of Cleves, his fourth wife, being divorced, Catherine Howard, his fifth, being beheaded, and Catherine Parr, number six, outliving him—but no more children. He had not had many illegitimate children, and in spite of 6 wives, his sum total of legal heirs was 3: Edward VI who died aged 16, Mary who reigned for five years (she had married Philip of Spain, but had had no children, though on numerous occasions she imagined herself to be pregnant) and Elizabeth who reigned until she was nearly 70, but had never married.

Of the 3 Tudor monarchs who had married, only the 2 Henrys had children. Henry VII had had 7, 4 of whom survived, but his Queen had died of puerperal fever. Henry VIII had had his 6 wives, but only 3 had become pregnant, their total pregnancies amounting to 11 only. Of these 11, 3 survived childhood (though 1 only to the age of 16), one died very early in infancy, and 7 were stillbirths, premature stillbirths, or miscarriages. 2 of the 3 surviving children had been difficult labours (1 most likely having ended in Cæsarean section) and 1 of his Queens also had died of puerperal fever. A satisfactory outcome of pregnancy appeared to be major obstacle in this family, and perhaps one might consider a history of congenital syphilis. There is, however, almost overwhelming evidence that this was not so. There were so many mothers, or would-be mothers involved, that one can dismiss toxæmia as a general cause of the trouble, and the Rhesus factor, too, can hardly be blamed. Whatever the cause of the difficulties and setbacks in their struggle to produce living infants, it does sound as if some of these Queens were in need of skilled obstetric care, and it is of course, more than likely that the gaps in the knowledge of this specialty were largely the cause of the trouble. What particular gap it is hard to say, but perhaps an obstetrician interested in ante-natal care might have gone a long way towards preventing these tragedies.

TABLE IV.—NORMANS AND EARLY PLANTAGENETS

Monarchs and their consorts	Pregnancies and children	Surviving to adolescence
William I and Matilda of Flanders	10 children	9
William II	Never married	
Henry I and Matilda of Scotland	2 children	2 (one drowned in White Ship)
Henry I and Adela of Louvain	0	0
Stephen and Matilda of Boulogne	5 children	4
Henry II and Eleanor of Acquitaine	8 children	7
Richard I and Berengaria of Navarre	0	0
John and Isabella of France	5 children	5
Henry III and Eleanor of Provence	9 children	6
Edward I and Eleanor of Castile	13 children	8
Edward I and Marguerite of France	3 children	2
Edward II and Isabella of France	4 children	4
Edward III and Phillipa of Hainault	12 children	10

Normans and Plantagenets (Table IV)

Passing back over the Wars of the Roses and internal strife and struggle originating from the descendants of Edward III, we go to 1066 when William the Conqueror came over here. William was the first of the 4 Norman Kings, and he had married Matilda of Flanders. This most able, energetic and learned Queen spent some of her time in England, and some in Normandy, moving about with her husband, except on those occasions when William left her to govern in his absence. During her busy life Matilda managed to bring up quite a sizable family. Nine months after her marriage her first son was born, and he was followed in fairly quick succession by 3 more sons and 6 daughters. A total of 10 children, all of whom survived to adult life, with the exception of 1 who died late in childhood, possibly it is thought of malaria, a disease which flourished in the low-lying parts of the country. After the batchelor King, William II, another and younger son of William the Conqueror became Henry I. Henry had married Matilda of Scotland, and by her he had 2 children—a small family in those days. It is interesting that, prior to his marriage, Henry had had a large selection of illegitimate children (he owned to 20 at least), then 2 by his first wife, and none by his second wife Adela. She, however, eventually married again, and had, according to the Chroniclers, "numerous progeny", of whom 7 at least survived and are recorded by name. The next king, Stephen, had also married a Matilda. She was Matilda of Boulogne, and they had 5 children, of whom 1 died in early childhood. She too had a very busy and responsible time during her husband's absences, and she was frequently left in charge whilst he was away fighting the Empress Maud, who was trying to win the English Crown. We understand that all these Norman royal wives were pleasing in appearance and character. They were devoted wives and wielded considerable power in the country, besides having a sound and practical knowledge of the running of a household and estate, and during times of war were themselves frequently responsible for the care of the sick and wounded.

The first Plantagenet King was Henry II. His wife was Eleanor of Acquitaine, a Princess of Provence, who was an extremely intelligent young woman, well versed in the arts, especially music and poetry. She had been married to the King of France, and had had two children. She said that her husband was more Saint than man and, having set eyes on Geoffrey of Anjou and his son Henry, she demanded a divorce from the Pope on the grounds of consanguinity (she was a fourth cousin), and as soon as this was granted she married Henry of England, when she was 31, and he was 19. By him she had 5 sons and 3 daughters. One died at the age of 4, but the rest survived, 2 to become kings of England. This Queen who had provided the King of France with 2 children, and the King of England with 8, also found time to travel both at home and abroad, and besides journeying around England and France had visited Palestine and Constantinople. She was virtually ruling England at the time of Richard Coeur de Lion's death, and remained active and energetic until she took the veil two years before her death at the age of 81. As her son Richard and his wife had no children, the crown passed to a younger son, John, who at the age of 32, had married a 16-year-old French Princess. Their 5 children all survived to adult life, the eldest son, Henry succeeding his father on the throne. Henry III had married another Provençal Princess, Eleanor, and their 9 children all survived infancy, though 3 died during childhood. These Provençal Queens kept up a high standard of elegance, and were patrons of the arts, and King Henry III was especially interested in architecture, his palace being the first royal residence to have glass windows. When the time came for a bride to be selected for their eldest son Edward, the King and Queen themselves set off for Bordeaux, and from there the Queen went on alone to Spain, and in due course brought back the 10-year-old Princess Eleanor of Castile. This small Princess and her husband lived for a time in Bordeaux, then after returning to England, set out on a Crusade. Eleanor was with her husband in Syria and Palestine, then after visiting her mother in Spain, returned to this country via Sicily, Rome and France. Three of their 13 children were born during this trip. The Queen herself died during one of her journeys round England, and her sorrowing husband ordered a Cross to be erected to the memory of his "Chère Reine", at each resting place on the route to Westminster; in Charing Cross, the name is still remembered. Eight children survived their mother. The King at the age of 60 married as his second wife Marguerite of France, who was 16 years old. After his death, his son Edward became King, and the story of Edward II's favourites, and his wife's infatuation for Roger Mortimer is a well-known one. The most important of the 4 children of this marriage was another Edward, Edward III who, with his wife Phillipa, provided through their descendants those future claimants for the throne, and the rivalry which ended in the Wars of the Roses. Queen Phillipa had married when she was 16, and 10 of her 12 children reached adult life. Here was another wise and industrious woman. Like Catherine of Aragon, she was responsible for an army which

defeated the Scots. On hearing that the King of Scotland had crossed the border, she rode to Newcastle, rode amongst the troops, waited for the successful issue of the battle of Neville's Cross, and the capture of the King of Scotland, then rode to the coast, and crossed to Calais to join her husband.

Looking back at the Norman and early Plantagenet Kings and Queens, one notices that a number of them had large families, and there were comparatively few infant deaths. They seemed to become pregnant, carry on with their busy lives, make long journeys lasting for some weeks, or a year or two, produce their children, attend to their education, and visit their various homes and estates. The expectation of life as long ago as the eleventh, twelfth and thirteenth centuries was poor, but in spite of this the royal families seemed to thrive surprisingly well. The Hanoverians, apart from visiting their native Germany, travelled very little, and were singularly lacking in a number of the better qualities. The Stuarts had married their wives from Denmark, France, Portugal and Italy, but apart from journeys into enforced exile had not themselves been conspicuous for journeying abroad. The Tudors had taken a real interest in their people (assuming they were of the right religion), and did move amongst them on their royal progresses around England, but they were not particularly unselfish, and the commoners whose homes were honoured by these royal visits were expected to put a great deal of their wealth into preparing sumptuous and lavish hospitality. Reverting again to the earlier royal families—I personally have a very real admiration for their Queens. They were well educated, interested in affairs of State, had a high sense of duty, and nearly all proved themselves to be most capable as wives, mothers and administrators. It seems to me that for sheer devotion to duty, natural acceptance of family life, contact with their peoples both at home and abroad, for enterprise, adaptability, and readiness to give so much of their lives in journeys by which they hoped to benefit their country, the Norman and early Plantagenent Queens, and their husbands, have, throughout history, never been equalled, far less surpassed, until we come to those descendants of Queen Victoria who are our ruling house to-day.

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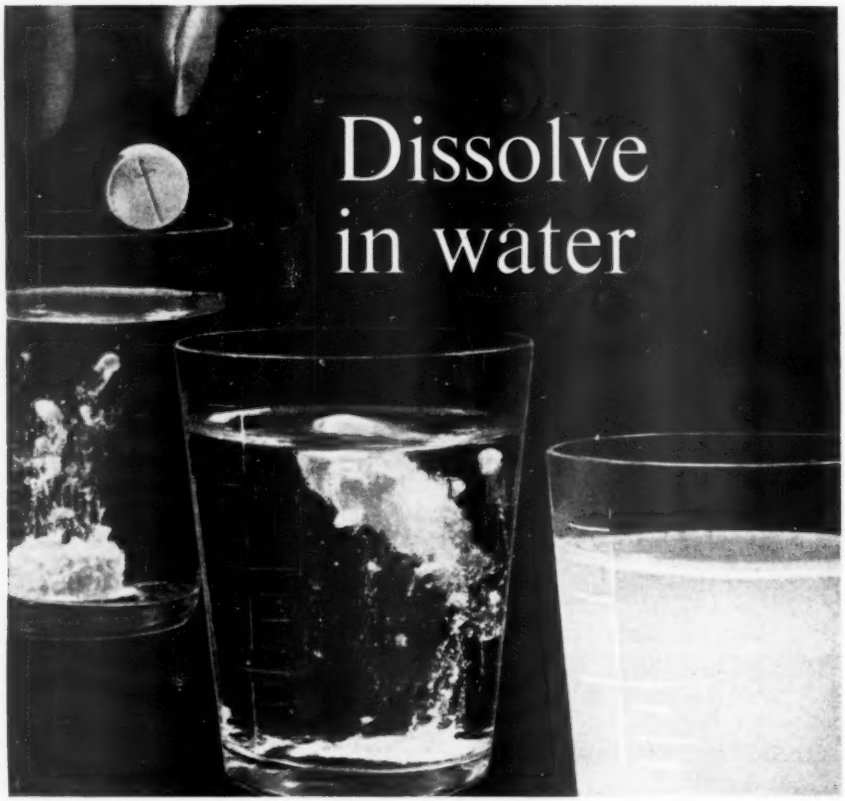

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Section of Psychiatry

President—R. STRÖM-OLSEN, M.D.

Meeting
October 13, 1959

Dr. R. STRÖM-OLSEN delivered his Presidential Address entitled **Some Problems in the Study of Psychotic Illness.**

Meeting
November 10, 1959

A Comparative Study of Psychiatric Classifications

By Professor E. STENGEL, F.R.C.P.
Sheffield

THE lack of an agreed classification of mental disorders has proved a serious obstacle to progress in psychiatry. It has made it impossible to draw valid comparisons between results of treatment carried out in different places, and is impeding epidemiological research. Dissatisfaction about the chaotic state of psychiatric classification has become quite general recently and has been voiced by all schools of thought. The World Health Organization took the initiative and, as a first step, appointed a temporary consultant with the task of carrying out a comparative study of classifications used in psychiatry to-day. His report was to form the basis of an attempt at establishing an agreed international classification of mental disorders. This had been tried before but had failed. It was part of the consultant's task to examine the reasons for that failure. The speaker was invited to undertake this study. No attempt was made to carry out a complete survey. The aim was to investigate present trends in psychiatric classification used for clinical, statistical and research purposes. In some countries no registration of psychiatric morbidity had, at the time of the enquiry, been carried out, while in others it was done very thoroughly. In several countries special committees concerned with classification and aiming at establishing uniformity within their national boundaries were at work. 58 classifications were collected. They were divided into two groups: (1) Those which had been used or recommended for use by public health authorities or learned societies, i.e. the official, semi-official or national classifications. (2) Those used only regionally or locally.

The International Statistical Classification of Diseases, Injuries and Causes of Death (I.C.D.) issued by WHO was recommended for use by all member states. However, the part relevant to psychiatry, Section V, failed to find general acceptance and was adopted only in Finland, New Zealand, Peru, Thailand and in this country. It differs from all other classifications by not presenting all mental disorders together. Some are listed in the context of other sections. For instance, puerperal psychosis is listed among the complications of the puerperium, general paralysis under syphilis, &c.

The American Psychiatric Association developed a classification of their own, the so-called A.P.A. Standard Classification (1952). Part of the nomenclature used in this classification was new. However, it cannot have had an easy passage either, because it has so far failed to be adopted by the State of New York which, from the point of view of psychiatric statistics, is the most important state of the Union. Unlike Section V of the I.C.D., the Standard Classification covers all psychiatric conditions. The users of this classification are greatly assisted by the "Diagnostic and Statistical Manual" issued by the American Psychiatric Association. This Manual contains a glossary of psychiatric terms. Thus the A.P.A. classification is better documented than any other. Its adoption by some other countries of the Western Hemisphere has been under consideration for some time. The American Standard Classification uses ætiology as the guiding criterion. Psychogenic ætiological

factors are accorded equal status with organic causes. The first section includes all psychiatric disorders in which an impairment of brain function can be assumed, however transient and of whatever origin. Although the involvement of the brain may be trivial and quite accidental to the main physical illness, it qualifies for inclusion into this section of "brain syndromes" which comprises all organic psychiatric conditions ranging from a state of slight alcohol intoxication to Alzheimer's disease and amaurotic idiocy. The logical advantages of this arrangement are obvious, though it resulted in the breaking up of traditional clinical groups of mental disorders. There was little left of mental deficiency outside the section of brain disorders, and of the psychoses only the schizophrenic and manic-depressive reaction types remained as a separate group. The section concerning psychotic disorders on the whole follows the conventional pattern. The term involutional depression was replaced by "involutional psychotic reaction". There is a so-called psychotic depressive reaction which is not referred to in the I.C.D. The section entitled "psycho-physiological autonomic and visceral disorders" contains many neurotic states with physical symptoms. The term hysteria was abandoned. The most controversial section is that concerning personality disorders which are divided into four subsections—personality pattern disturbance (e.g. schizoid personality); personality trait disturbance such as compulsive or aggressive personality; sociopathic personality disturbance including the antisocial, the perverts and the addicts; and, fourthly, a miscellaneous group containing special disabilities such as speech disturbance, &c. The glossary is helpful but sometimes ambiguous. It does not, for instance, give clear guidance about the classification of paranoid psychoses.

The Canadian Classification is a shortened version of the I.C.D. The number of categories of the psychiatric section of the I.C.D. has been reduced by 4. The French Standard Classification follows on the whole the classification of Kraepelin, with an even stronger emphasis on clinical symptomatology. In Germany a variety of classifications are in use. The older ones have no independent section for the neuroses which are included in the two categories of psychopathic personalities and abnormal reactions. However, in the more recent classifications the neuroses again figure as independent categories. Japan has, in matters psychiatric, remained under German influence. The classifications in use in the Scandinavian countries are of particular interest as Scandinavian psychiatrists have given the problem of classification and diagnosis a great deal of thought. Their orientation is frankly symptomatological. A special feature is the emphasis on psychogenic psychoses and behaviour disorders. In Switzerland and Portugal a shortened version of the French Standard Classification is used. The classifications used in the Soviet Union are based on classical European nosology to which Pavlovian concepts are applied. It is noteworthy that anxiety neurosis does not figure among their clinical categories. In the concept of psychogenesis of the Russian authors, "traumatism" rather than conflict is assumed to be the pathogenic factor. Hereditary factors are accorded relatively little importance. The basic approach is neurological and neurophysiological.

Among the seventeen sections of the I.C.D., Section V is the only one which has been almost generally rejected. The speaker made it his task to investigate why it met with such a poor reception. He also tried to find out how it had been working where it had been in use. A great variety of critical comments were received from organizations and individual psychiatrists. One of the most common complaints was lack of comprehensiveness. Psychiatrists resented having to go outside Section V to classify common psychiatric conditions. Scandinavian colleagues criticized the absence of the category of psychogenic psychoses and of other concepts they regarded as important. Others found it unwieldy and too complicated. Henry Ey called it incoherent and inconsistent with regard to basic principles. In his view, most classifications in current use were mere enumerations and nomenclatures. It must be admitted that Section V of the I.C.D. has many irritating features. It is headed "Mental, Psychoneurotic and Personality Disorders". "Mental" in this context means psychotic, surely a blatant terminological anachronism. Some categories are too inclusive and lack subclassifications. The subclasses of the categories of personality disorders have been criticized for not being mutually exclusive. Child psychiatrists have felt that Section V of the I.C.D. served their requirements very inadequately.

Section V of the I.C.D. has been used in this country since 1948. This provided an opportunity for obtaining the views of some of those who worked with this system and also for examining its potential usefulness for the research worker. The data obtained with the help of this classification show many bewildering discrepancies. For instance, in 1949 the diagnosis of paranoid psychosis was made in the Manchester Region only 14 times among 3,212 admissions, while

in other regions with approximately the same number of admissions, it was made 74, 82, 100 and 125 times respectively. There were similar discrepancies in other categories and some were very little used. Obviously, the I.C.D. had failed in its purpose of recording relevant data reliably. There were at least two reasons for this: first, the system had been only partly accepted by those who had to provide the data, and secondly, there was insufficient agreement about the meaning and scope of the categories. Unfortunately, the recommendation of the 1950 WHO Expert Committee on Mental Health, that a glossary of descriptive definitions of Section V should be compiled, has never been implemented. The 1955 Revision brought some slight modifications in the categories concerning mental deficiency only. It became clear from the enquiries that the existing I.C.D. had no prospects of being generally accepted in its present form as far as psychiatry was concerned. The same applies, for other reasons, to the American Standard Classification.

Principles of classification.—A classification divides a given set or class of objects into subclasses which should be mutually exclusive and jointly exhaustive. In medicine there has been a gradual development from a symptomatological to an ætiological emphasis. In psychiatry, the application of the principles underlying classification meets with difficulties, owing to the lack of objectively verifiable concepts. The material the psychiatrist has to classify consists neither of disease entities in the strict sense, nor of people, but of a variety of disorders or reactions some of which are not mutually exclusive. There is much to be said in favour of operational definitions in psychiatry, i.e. definitions based on agreed criteria and used for specific purposes such as classification. In fact, many of the present nosological concepts are no more than operational definitions. Schizophrenia, then, as an operational concept, would not be an illness, i.e. a biological reality with which it would be wrong to tamper, but an agreed operational definition for certain types of abnormal behaviour. The same applies to such concepts as psychopathy, &c. From the point of view of classification, therefore, the question would not be what schizophrenia or psychopathy are, but in what meaning those concepts should be used for the purpose of diagnosis and classification, i.e. for the purpose of communication. Those who find it difficult to accept this frankly utilitarian attitude to psychiatric classification can be referred to Kraepelin's comments to the last version of his classification: "I want to emphasize that some of the clinical pictures outlined are no more than attempts at presenting part of the material observed in a communicable form".

What have been the criteria, or principles, or dimensions, or axes underlying psychiatric classifications? Kraepelin's orientation has been described as one of empirical dualism. He combined cerebral pathology with psychopathology. His broad division of mental disorders into organic, probably organic and/or constitutional, and psychogenic, is still a basic feature of most classifications to-day. It did not occur to Kraepelin that psychogenic ætiology disqualified from membership of the class of mental disorders. This is the characteristic feature of Kurt Schneider's broad division of the material. To that author the concept of illness applies only where organic changes exist or can be postulated with confidence. Other mental disorders are only abnormal varieties of sane mental life. According to Schneider, there are no neuroses but only neurotics. The concept of neurosis as a psychopathic reaction had a considerable influence on psychiatric theory and practice in Germany.

Adolf Meyer's classification followed from his concept of mental disorder which was fundamentally psychopathological. Kleist's system is consistently ætiological. The schizophrenias are classified with the cerebral degenerative diseases; the neuroses are cerebral dysfunctions, with psychogenic factors playing only a secondary role. Leonhard's classification of the endogenous psychoses follows the same line. Henry Ey's classification is fundamentally psychopathological, with a psychophysiological bias and an existentialist philosophy. He views mental disorders as manifestations of disturbances of two variables, the level of consciousness and the functioning of the personality. The first group, disturbances of consciousness, includes all acute psychoses including manic-depressive attacks, while the rest forms the second group. The scheme is very clear and logical, but some of it is at variance with clinical realities. There is no representative psychoanalytical classification, though Menninger has revived the old unitary concept of mental illness. To him the various mental disorders differ only by the degree of regression of mental functions. In many classifications, consistency is maintained by the postulation of a certain type of ætiology, e.g. of an organic cause for schizophrenia. The kind of ætiology implied in these classifications is that of a single causality which is by many regarded as inapplicable in psychiatry.

There are considerable differences in the classification of paranoid reactions. Only a minority of the classifications have the category of involutional depression. It is needless to say that the discrepancies are most serious in the categories of the neuroses and personality disorders.

Differences of opinion about the relative weight of ætiological factors singled out as criteria for definition are responsible for a number of divergencies. The question whether psychogenic psychoses should be given the status of an independent category is a case in point. Such a category is likely to be opposed by the organicist, who would accord psychogenic factors only a minor role in the ætiology of the psychoses, as well as by the psychodynamically oriented psychiatrist. The latter would argue that such a category implies the absence of psychogenic factors in the ætiology of the psychoses not termed psychogenic. Similar differences of basic concepts enter into the question of the relationship between the neuroses and the psychopathies. A small number of classifications attempt to classify along two axes, i.e. the clinical and the ætiological, at the same time.

It may well be asked whether, in view of the existing difficulties and the failure of the I.C.D. to find general acceptance in psychiatry, any other classification would have prospects of success at the present time. In answer to this question, it can be stated that there has never been as strong a demand for an international classification of mental disorders as there is to-day. However, it still remains to be proved that psychiatrists are willing to adopt such a classification at the price of some inconvenience and concessions.

Those concerned with devising an international psychiatric statistical classification will have to make up their minds about two problems: (1) Is it essential for an international psychiatric classification to be preceded by, or even be the outcome of a generally accepted international psychiatric nomenclature? (2) Is it essential for such a classification to be preceded by an agreement on basic diagnostic concepts?

Desirable though the adoption of a common nomenclature might appear, such an agreement is not an essential prerequisite for a practicable and generally acceptable classification. Probably considerations concerning nomenclature have in the past interfered unduly with the requirements of classification. The difference between a statistical classification and a nomenclature tends to be overlooked. A nomenclature, being a list of approved terms for describing and recording observations, has to be extensive and unlimited in scope and detail to allow for the faithful recording of the manifold individual variations of ill-health. A statistical classification, on the other hand, is concerned with groups of conditions whose peculiarities have to be fitted within a limited number of categories chosen for their usefulness for the numerical study of disorders. The functions of a nomenclature and of a statistical classification are, therefore, in some respects opposed to each other. It is even conceivable that a statistical classification would dispense with nosological terms altogether and use numerical or other symbols. However, there is no need for such a device. There exists sufficient agreement on basic terminology for a generally acceptable classification of mental disorders to be drawn up. Possibly such an agreement may prepare the ground for a common nomenclature. But the latter would be a much more ambitious and complex undertaking than a classification which would have to be a relatively simple instrument of communication. It may even be argued that a generally adopted detailed psychiatric nomenclature may at the present time have an inhibiting effect on psychiatric thought.

The second question concerns agreement on diagnostic concepts. The view has often been expressed that the lack of such an agreement is bound to defeat the purpose of any national or international classification. Comparability of diagnostic data presents a serious problem in psychiatry. The reliability of diagnosis has been found to be very low in many areas of psychiatric morbidity. Some investigators, however, have found a surprisingly high reliability, especially where psychiatrists shared a similar orientation. Psychiatrists have for some time paid too little attention to their diagnostic concepts which often differ considerably, even among members of the same institute, without their being aware of it. If, for instance, some psychiatrists regard recovery as incompatible with the diagnosis of schizophrenia and others do not hold this view, and if they have failed to make it clear to each other that their diagnostic concepts differ fundamentally, how can they be expected to agree? But apart from these difficulties, which could be considerably reduced, the reliability of psychiatric diagnosis will remain limited in those categories where no objective criteria can be employed. However, these difficulties can be overstated. The adoption of operational definitions should go some way towards reducing disagreements on diagnosis. I believe that no explicit agreement on

diagnostic concepts is necessary, provided that the existence of different concepts is recognized and guarded against, and provided that operational definitions are adopted for the purpose of classification. A statistical classification of mental disorders, to be acceptable internationally, will have to avoid the impression that it aims at influencing psychiatrists all over the world along certain lines which many of them may not wish to follow. The requirement of neutrality in the controversies between various schools of thought imposes considerable limitations on an international classification. It has to be based on points of established agreement. This is why it cannot be ahead of its time. It can at present be no more than a tool of communication for a limited range of data such as the incidence and prevalence of certain mental disorders. There is no reason why an international psychiatric classification should not coexist with regional or local classifications, many of which have valuable functions in research and administration. Such classifications may stimulate the study into new relationships and thus advance knowledge. The only proviso would be their easy convertibility into the international system. That this is practicable has already been proved. A glossary with operational definitions of the various categories would have to be available from the beginning.

It has often been said that a classification has above all to be consistent with regard to the criteria of differentiation. Such a demand is unreasonable at the present state of psychiatry. No psychiatric classification can help reflecting the patchiness of our knowledge. It will have to be partly ætiological and partly symptomatological, because these are the criteria by which psychiatrists distinguish mental disorders from each other. No classification can meet every criticism, but even the best cannot serve its function unless all those participating in its application know it and want to make it work. It is essential that the psychiatrists supplying the diagnostic data should be familiar with the statistical classification in use and with its purpose. This is the exception rather than the rule to-day. Many psychiatrists seem unaware that their diagnoses are more than private observations concerning only themselves and their patients.

One of the recurrent criticisms of the I.C.D. and similar classifications has been the lack of provision for the recording of diagnostic formulations. The same difficulties exist in other fields of morbidity and it is doubtful whether a statistical classification which could serve this purpose can be designed at present. The I.C.D. provides for related and unrelated additional diagnoses. Classifications which allow for the recording of two or more dimensions have been recommended, but no information about the use of such systems has so far been available. Those concerned with the revision of the I.C.D. will be well advised to make Section V comprehensive. Theoretical objections against such a change are far outweighed by the practical disadvantages of the present arrangement. The question how agreement on a drastic revision of Section V could be reached, is under active consideration. It will be necessary for suitable proposals to be submitted in good time before the next Revision Conference in 1962. It may be advantageous if pilot studies with alternative classifications thought to be suitable for international use were undertaken before final recommendations were made. Agreement will be reached if the advantages of an international psychiatric classification are generally recognized, if it is realized that a classification is not the embodiment of scientific truth but a code for practical use, and if it is understood that such a code can perfectly well coexist with other systems of classifications serving specialized purposes. It is hoped that in a few years' time there will be an international psychiatric classification which will enable psychiatrists to communicate with each other better than they can to-day.

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Discussion

Miss Eileen Brooke (London): It was with considerable rejoicing that we at the General Register Office learned that Professor Stengel was making a survey of Classifications of Mental Disease. For ten years we have been struggling to make the International Classification work on diagnoses assigned to patients admitted to Mental Hospitals, and in other morbidity work.

Statistical comparisons within and between countries, which have been very helpful in the study of other diseases, might help also in the study of mental disorder. But for this it is essential either that everyone should be calling the same thing by the same name, or, if different diagnostic terms are used, there should be exact correspondence between them. There are two places where differences may arise: in the diagnosis, or in the coding done in the statistical office.

To test the efficiency of the coding an exercise was begun between Canada, England and the U.S.A. From the routine data, each country would select 200 consecutive but different diagnoses, and code them by the I.C.D., the A.P.A. classification and the Canadian abbreviation of the I.C.D. The results would then be collated, and show how much variation could be attributed to coding. It was also proposed to see if terms not covered by the classification in use in one's own country could be coded by a different classification. We carried out our part and the U.S.A. have now begun work on our list. In their hospitals all diagnoses not in the A.P.A. are referred back to the psychiatrist.

However, the A.P.A. classification gives corresponding code equivalents in the I.C.D. We coded the 200 diagnoses first by the I.C.D., then independently by the A.P.A., and used the A.P.A. equivalents to translate back to the I.C.D. In theory we should then have arrived back where we started. In practice, we got agreement in 84 out of 205; just over 40%. Counting only 3-digit categories for schizophrenia and manic-depressive reaction increased the agreement from 40 to 47%.

We next took the three subdivisions of Section V of the I.C.D.: psychoses, psychoneuroses and disorders of behaviour, character and intelligence. Of 107 originally in the psychoses group, 77 (72%) returned there after their journey through the A.P.A. Of 39 psychoneuroses, 23 returned to the same group, 59%, and of 30 in the B.C.I. group, 26 returned to the same group, 87%. This suggests that whether the I.C.D. or the A.P.A. is used, classification into these three main categories is not completely haphazard. Were it not for considerable confounding between 301, manic-depressive reaction and 314, reactive depression, agreement would be more substantial.

A cohort study of what happens to a patient in the two calendar years following his date of first admission has shown two things of particular interest in relation to diagnoses. The curves for the percentage remaining alive and in hospital at three-monthly periods for schizophrenia and manic-depressive reaction behave in different ways, but for each disorder the curves for single and ever-married males and females behave in the same way. The same is true for the total percentage time in hospital irrespective of the number of visits. This supports the contention that, on the whole, two different types of illness are being recognized and diagnosed.

In the second half of 1955, 293 patients were admitted who each had 4 hospital admissions in the two years (Table I). Each patient could enter up to 4 different hospitals and was diag-

Table I.—Patients Entering Hospital 4 Times in Two Years from Date of First Admission in 1955

	4-digit categories					3 digits only for schizophrenia and manic-depressive reaction				
Hospitals	Diagnoses					Diagnoses				
	1	2	3	4	All	1	2	3	4	All
1	57	92	66	11	226	92	92	37	5	226
%	25	41	29	5	100	41	41	16	2	100
2	3	29	19	8	59	15	25	15	4	59
%	5	49	32	14	100	25	43	25	7	100
3	—	3	3	1	7	—	3	4	—	7
4	—	1	—	—	1	1	—	—	—	1
Total	60	125	88	20	293	108	120	56	9	293
%	20	43	30	7	100	37	41	19	3	100

nosed 4 times. The period of two years might be expected to set some limit to the number of separate mental diseases from which the patient could suffer.

Using 4-digit categories where they occur, only 25% of those entering the same hospital retained the same diagnosis throughout; 43% of all patients received two diagnoses. Using 3-digit categories for schizophrenia and manic-depressive reaction, 41% entering the same hospital at each visit had the same diagnosis. The number with 4 different diagnoses was reduced from 20 to 9.

When we take the three broad groups of Section V, we find that, despite variations, 59% remained in the psychotic group throughout. There were 48 patients consistently labelled manic depressives, and 39 schizophrenics, compared with 16 who alternated between these diagnoses. Only 5 patients out of 293 had diagnoses from all three groups.

We intend to continue these studies to see, for example, how far the first diagnosis is confirmed by subsequent ones, and, as we push the survey period on to five, instead of two years, whether the variation increases or whether the diagnosis becomes stabilized. We are also anxious to see whether certain combinations of diagnoses recur, and if so, whether they are meaningful to the psychiatrist.

Dr. Frank Fish (Edinburgh): Psychiatry to-day is roughly in the same position as general medicine was in the middle of the eighteenth century. The nosological differences in general medicine were not solved by arguments but by scientific investigations. The correlation of clinical findings with morbid anatomy was initiated by Morgagni in 1781. Psychiatry still awaits its neurophysiological Morgagni.

A false contrast between psychodynamics and diagnosis is often made. This may be regarded as an expression of the antithesis between the individual as a unique person and as a member of a group. Thus Kierkegaard (1938), the manic-depressive founder of Existentialism, stressed the uniqueness of the individual and opposed the scientific study of the mind.

The contrast between psychodynamics and diagnosis can be understood from another point of view. The psychodynamic psychotherapist finds that the diagnostic categories do not express the richness of morbid psychological events. The clinical psychiatrist is contemptuous of his psychotherapeutic colleague's neglect of basic common features of psychiatric syndromes. There is no real contrast between psychodynamics and diagnosis since both are necessary for the adequate handling of our patients. Often psychodynamic formulations are merely old diagnostic categories expressed in a new jargon. Freudian psychodynamic formulations have recently been restated in Heidegger's terminology (Binswanger, 1953, 1956).

Despite criticisms of the unscientific nature of psychiatric classifications we still need such classifications as a framework for clinical work and for further investigation. The temporary nature of the framework must never be overlooked.

My own interest in classification began with an interest in the clinical features of chronic schizophrenia. Kleist (1943, 1949; Fish, 1957*a*) and Leonhard (1936, 1957; Fish, 1958*b*) had described the clinical features of chronic schizophrenia in great detail and had classified the clinical pictures in a very exhaustive way. I found (Fish, 1957*b*, 1958*a*, *b*) that both these schemes were useful but that of Leonhard (1957) was more precise and easier to use. In the course of my work I found that the use of the ideas of Kleist and Leonhard increased my knowledge and understanding of chronic schizophrenics. I found, like these workers, that certain symptoms and signs are repeatedly found in any large group of schizophrenics. The presence of these symptoms in chronic schizophrenics in Britain, France, Germany and Norway raises the question why such symptoms repeatedly occur independently of the culture as almost automatic phenomena. A neurophysiological, pharmacological and psychological investigation of these symptoms is needed. Astrup (1957, 1960) has, in fact, shown that results of certain physiological tests differ in different Leonhard subgroups of schizophrenia.

Leonhard's scheme is very useful in any investigation of chronic schizophrenics because it ensures careful examination and puts the results of such examination in a readily communicable form. Nevertheless despite its usefulness it could not be recommended as a part of a new international classification. These detailed special classifications have a part to play in research but when a new international classification is established we must all be prepared to use it as well as our favourite private classification so that a reasonable amount of information will be avail-

able to any worker acquainted with the international classification.

An agreed international classification will make interchange of results of investigations much easier and will bring about a badly needed interchange of ideas between different national schools. An international classification will need an explanatory manual similar to the "Diagnostic and Statistical Manual of Mental Disorders" (1952) published by the A.P.A. Such a manual will define the various disease entities and correlate them with diagnostic categories used in other classifications. Perhaps this diagnostic manual could be supplemented by reviews of the teachings of different schools of psychiatry in certain selected special fields in psychiatry where there is much disagreement. It is, I am afraid, too much to hope that this interchange and clarification of views might finally lead to an International Handbook of Psychiatry.

I have been obliged to use the present International Classification of Diseases in psychiatry since 1952 and I have never found it to be satisfactory. The lack of adequate definition of the diagnostic categories is infuriating. The failure of this classification should not, however, be taken as a proof of the uselessness of all classification. I am sure that a much more flexible and workable classification can be agreed on internationally.

Finally I would like to point out that we are faced with a paradoxical situation. An adequate psychiatric classification can only be based on ætiology but we can only acquire knowledge of the ætiology of psychiatric disorders by using a classification not based on ætiology. No wonder Jaspers (1946) has said "All schemes of diagnosis must remain a torment for the investigator!"

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Section of General Practice

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Meeting
November 18, 1959

DISCUSSION ON THE AGEING MIND

Dr. Annis Gillie (London):

Maturing involves ageing both in mind functions and in tissue changes. The critical and intellectual capacities, and degrees of adaptability, vary widely in elderly men and women. The degree of deterioration of mental ability varies in the amount of change from an individual's capacity at its best, and needs to be related to it. If age is to be contemplated as an active and satisfying phase of life, it is important to examine the circumstances that favour the retention of those qualities which will help to compensate for the inevitable process of degeneration.

In the old Chinese civilization so recently ended, the aged were revered. An element of holiness surrounded them, and even senility was regarded as sagacity. These oldest members of the family were preparing to join their ancestors and were already honoured in life as they were about to be in death.

In our Western civilization only rarely is value associated with old age. Homes no longer hold three or even four generations. The current attempts to deal with the older population have produced only a partial social solution, complicated by the drawbacks of the resulting segregation. The majority of the young find little pleasure in the society of the aged, and old people are terribly aware of this and sensitive about it. As long as husband and wife are together loneliness is mitigated, and boredom for the woman is rare since she continues to use her domestic skills. The single old person, especially the widower, not only loses daily companionship, but the sense of being a part of society as well. For most ageing men and women this fear of uselessness and boring isolation is far more insistent than the fear of death, and it is in isolation that mental deterioration most rapidly occurs. However, where the social environment remains good (even if reduced to a society of two) any abrupt change in mental capacity or social behaviour is almost always the result of physical morbidity—a silent coronary attack, a mild cerebral episode, an undiagnosed neoplasm. The family doctor's alertness in discriminating between these two groups is an important factor in the prognosis and rehabilitation of many elderly patients.

The Nuffield Unit for Research into the Problems of Ageing has devised methods for estimating some of the mental faculties that diminish with increased age. Memory is a complex process, involving the ability to understand something of what is to be remembered. This ability decreases with age. The surface retention of the fact to be remembered, displaceable at any age, is much more easily lost in the elderly—especially if an activity, however trivial, comes between the memorizing and the need to recall the fact. In addition the very multiplicity of past memories seems to be unfavourable to the retention of new ones. All of this diminishes the capacity for learning new skills. However, once the deeper layer of memory is used and the memories organized and codified (an active intellectual process) then retention can still be adequate and becomes an addition to the reserves of past years.

Short-term memory is always involved in any practical activity and often has to be retained to be used at a later stage. The old person fills the kettle, puts it on the gas, goes to look for the matches and forgets that the gas was turned on. What is the telephone number that was looked up and is now being dialled? This short-term memory is essential in many industrial processes and also at a higher intellectual level in manipulating a complexity of data.

Impaired short-term memory also interferes with the speed and accuracy of making complex movements of objects in space. This can be very far-reaching and emphasizes the importance of familiar and simple surroundings for the aged. Short-term memory impairment is evident in the experienced car driver who can deteriorate dangerously due to the difficulty of recalling and associating the facts observed while driving. This is an important factor when considering the transfer of an elderly industrial worker to lighter but unfamiliar work. Complicating and adding to this difficulty of memory is a slowing-down during the performance of a succession of movements. The delay apparently occurs at the point of change and is due to an increased physiological resting period. The switch-over involves a bigger lag in time as age advances and the lag increases with fatigue or any physical impairment. If the pace is forced the impulses may be blocked

altogether and result in a breakdown of activity. Diminished acuteness of the special senses is an additional drag. All this results in the obvious unsuitability of older people for any form of assembly work, however light and simple, where the maintenance of an average speed is essential.

Any abrupt change of a regular activity or surroundings can interfere seriously with an old person's capacity. Similarly, undue self-criticism and attempts to analyse or alter skills long established by routine may contribute to a breakdown.

The touchy temper of ageing people has complex causes. Growing rigidity of habit and outlook can result in an intense distrust of change, especially in those whose lives have run along a confined path. With this is coupled the fear that change will be inevitable when independence decreases—although there is now less fear of poverty there is a terror of becoming institutionalized. The knowledge that almost 95% of the aged in this country manage to live in their own or their relatives' homes helps to reduce the development of this fear. Awareness of failing ability can result in resentment towards offers of help that draw attention to it, or in an access of self-pity when help is not forthcoming. Above all, loneliness and a feeling of being unwanted and, worst of all, not needed, can breed a brooding melancholy.

If all this is on the debit side there are also compensations as life advances, especially in using the less measurable functions of the mind. Large reserves of latent cerebral function can be developed before old age advances. It is in middle age that opportunities need to be taken to stretch and activate the already ageing mind. A subsidiary and later an alternative line of work, or study of a language or a craft, which can be continued much longer than the hitherto all-demanding job, are important. People with a high level of education or skilled craftsmanship show least deterioration in old age—partly because of the extent of their intellectual and co-ordinated activities, and partly because their work is often independent of any arbitrarily set pace.

Experience leads to the economy of both effort and performance. Tricks of easier function, whether mental or physical, however slowly acquired, can become automatic. The next move is planned in advance and strategy, deliberate or unconscious, can conceal diminishing capacity by reducing fatigue and clumsiness even with unfamiliar work, provided the pace is not forced. The collating and retaining of memories make them more readily available. The deliberate exercise of mental reserves can lead to easier storage and mobilization of memories and conclusions through many years of the ageing process. At highest levels of intellect the conclusions based on experience are more apparent as the perspective of past life lengthens and detachment of the self increases. Thought processes which precede the expression of a valuable opinion often appear to be telescoped in later years, partly as a result of practice, and partly from the use of strategy in assembling well-stored data. An example is the gift for successful spot diagnosis of some senior physicians.

This very richness of experience is not without its drawbacks. In facing a new situation the abundance of experience and multiplicity of available responses may make selection difficult and result in further slowing. There is the serious risk, too, that previous success with a certain thought pattern may come to dominate even a very able mind and lead to limitation and rigidity.

Selection is an art to be practised long before old age is reached. Selection of work that can be continued beyond the expected age of retirement may be one solution, selection of subsidiary interests to fill retirement more happily than the continuation of unsuitable work another. Methods of avoiding the overworking of short-term memory are nearly as vital. Selection of one's own pace in performing unfamiliar tasks must be combined with the confidence that, given time, the pace will improve. The development of tricks and manœuvres to compensate for diminished sensory acuteness often requires skill and great determination.

Often the family doctor is the only person with both the knowledge and the authority to indicate the need for planning a fundamental change. He is the one who can accurately assess the slow withdrawal of his patient and make constructive suggestions for the reorganization of his life. It is very difficult to rehabilitate an aged mind that has lost all appetite for life; it is relatively easy to redirect interests that have not dimmed too appreciably.

Dr. T. N. Rudd (Southampton):

Mental Supports in Old Age

We are living in an age where more organized effort is being made than ever before to improve the welfare of old people. The high prevalence of senile mental changes is, therefore, all the more disturbing, suggesting that our intense social and economic efforts are quite inadequate to counterbalance the present-day "desocialization" of the elderly population. We have gained years of life at the expense of a valid position in society.

One hundred years ago, Robert Browning wrote "We live by admiration, love and praise". We need, in other words, to obtain our satisfaction in life from human relationships rather than provisions for our physical needs. This is a disturbing thought to most people, as it is easier and more comfortable to increase pensions than have a human relationship with an older person.

Throughout the productive phase of life, men and women obtain satisfaction from their capacity to earn, their professional or craft skills, their family relationships and their place in society. Financial success, the respect of the community and a happy home life are the ambitions of the average individual. Failure in any one of these categories is often compensated for by increased strivings for success in the others. At the age of retirement, however, an entirely new situation develops. For certain individuals retirement even from spare-time occupations or hobbies at any age can present a difficult problem in adjustment. During the later years when retirement is obligatory, such adjustment becomes unusually difficult and is often coincident with other life-stresses. Work satisfactions are suddenly withdrawn, financial restrictions ensue, death often contracts the circle of family and friends, while the esteem the community accorded the "producer" is changed to an equivocal approach towards the "non-contributor". For many men retirement is the last straw breaking down an adjustment previously maintained only with difficulty: while good health and intact family relations may support a retiring man for a certain time, the disintegration of his personality has already begun. Women are in an easier position, in the sense that, for them, the battle of life goes on. They still have to make "both ends meet", to provide and cook the food and keep their men contented. The woman's primary role as housewife thus remains intact even though her efficiency may have declined, and this may well be a fundamental factor in preserving her from senile dementia.

The honouring of old age has markedly disappeared since we changed from a patriarchal civilization to one in which youth-values are unduly emphasized. In primitive tribes the aged maintained their hold on society in well-recognized ways. When cultural and religious attitudes failed to provide respect the old person could, and did, sell his experience and craft technique for beasts or corn (Simmons, 1945). When all else failed, the ageing man's very proximity to death invested him with considerable power for he was approaching another life from which he could effectively aid or harm those who were still living. Unfortunately what was once the old man's asset, age itself, is now his greatest liability. Age is no longer power: in a world of changing techniques, age is weakness, loss of respect, tolerance instead of honour. The fear of being a lonely, frustrated, dependent old person is very strong and has given rise to a little-recognized psychological phenomenon of the greatest importance to our civilization—"elder-rejection".

The psychological repression of unacceptable mental thoughts is a familiar one: it is also well known that such repressions can return to consciousness in a distorted form, affecting one's conduct and attitude to life. Civilization creates many fears. The fear of old age is particularly intolerable to many people, and thus strongly repressed. It does, however, reappear in the attitude of disparagement of the aged, more often expressed indirectly than put into words. The result is a prejudice, often unreasonable, against old age and older people, against parents and parents-in-law, and against aged persons in hospital or in the community. The attitude also extends to the care of the aged sick and the practice of geriatrics, with feelings of distaste and futility toward efforts to help the old. Compensation mechanisms ensue and it is at least possible that the prevalent over-concern with pensions is an expression of the hope that someone else's money will be an effective substitute for a personal duty to the old people in one's own family and community.

The real danger of elder-rejection is, however, the halt that it calls to the mature person's preparations for growing old, with the result that one day he suddenly finds that his life has changed and he is quite unable to adapt to this new situation.

The loss of his accustomed life satisfactions may come as a sudden blow to the unprepared newly-retired individual, and with it the realization that in rejecting old age he is himself being rejected. This can lead to an attitude of self-rejection, a dangerous surrendering to one's environment, rather than the normal healthy pugnacious protection of self-interests. Feelings of guilt at this stage may produce a sense of personal unworthiness. From this the advance into senile dementia can be traced (Linden, 1957). Self-esteem diminishes, psychological defences crumble, and conscious anxiety and intrapsychic terror develop. Withdrawal, psychotic regression and infantile defence mechanisms now complicate the picture and lead to the familiar state of apathy and disintegration of the personality.

If such cases are to be salvaged a vigorous approach in the early stages is mandatory, but real success lies in sound measures taken in the

pre-retirement age group. The basis of our approach, whether in hospital or in the home, is the restoration of self-esteem, the replacement of old satisfactions with new ones and a re-integration with the community, even when the community concerned is only the limited one of a hospital ward or an old person's home.

The integration of the individual into the community is the main aim, and with this in view, the abolishment of such antisocial symptoms as urinary and fæcal incontinence and senile confusion becomes doubly important. However, improvement of physical and mental health is only a step towards integration: the value of a healthy body is that it shall be able to "go places", and such places are themselves only of value in promoting integration so long as they provide a sympathetic and helpful atmosphere.

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Dr. E. Beresford Davies (Cambridge):

The commonest psychiatric disorders among elderly patients are affective psychosis, confusional psychosis, and dementia. Analysis of mental hospital populations nowadays shows that about half the patients are likely to be over the age of 65; of these there are many more women than men. A certain number of these patients have been in hospital for a very long time. These are the survivors of schizophrenic admissions in the earlier part of their lives. The hospital environment evidently acts in a protective manner, so that their longevity is increased. For the present they may be dismissed because they are seldom the responsibility of any authority other than the mental hospital.

I would now like to turn to certain statistics, for which I am indebted to Dr. David Clark and Dr. R. A. Pargiter; they are based upon investigations carried out at Fulbourn Hospital, in the Cambridge Psychiatric Service, between 1954 and the present time. Some of the inferences from these figures are my own. Fulbourn Hospital is one where the geriatric problem has caused a very considerable burden because the hospital has unusually severe overcrowding. In March 1959 half of the women were over 60, and almost one-third over 70. Between October 1954 and January 1959 the admissions of patients over the age of 65 rose from 29½% of the total hospital population to 35%. This increase has been accounted for almost entirely by the admission of women.

If we take the decade 1948 to 1958, the increase in annual admissions of patients over the age of 65 is from 67 to 160. In the year November 1956 to November 1957 there were 87 admissions of persons over 70; of these 33 were discharged, 19 died, and 35 remained in hospital. The diagnostic classification of these 87 admissions was: mainly affective illness 33; mainly organic illness 38; mixed 16.

As one would expect, most of the patients discharged were in the first category, and most of those remaining in hospital were in the organic class. One of the most interesting points about this group of patients was the care they had received before they came into hospital. A striking differential in admissions expressed in rates per 10,000 of the population was shown. The closer the patient lived to the mental hospital the greater was his or her chance of being admitted there rather than somewhere else. The better the facilities for old people generally, the less likely they were to be admitted to the mental hospital. Proximity and convenience therefore may play a greater part in the admission of elderly patients to mental hospitals than purely medical considerations. As might be expected, patients with mainly affective illnesses tended to be admitted to the mental hospitals irrespective of their domicile, or the general facilities available for elderly patients. However, a large number in the mainly organic class, for whom undoubtedly other and better arrangements could have been made, were also admitted to the mental hospital.

The care of the elderly in a mental hospital has been revolutionized in recent years. It is not at all uncommon to use electroplexy and, of course, the more modern drugs such as imipramine in patients over 80, with satisfactory results. In general these patients should not have electroplexy on an out-patient basis for, quite apart from the problem of providing home care, the additional risks to the ambulatory patient rise very steeply after the age of 65.

The most important drugs are chlorpromazine, the other promazines, perphenazine, and the mono-amine oxidase inhibitors. Pride of place must be given to chlorpromazine, for it was the first drug in this field and remains the most effective in certain conditions. I refer especially to the treatment of those states of excitement and agitation among the cyclothymic patients, and to paranoid ideas with their concomitant hostility and awkwardness in paraphrenic elderly patients. Chlorpromazine appears to act almost specifically in lowering the tension in these patients. Sometimes the paranoid ideas disappear entirely; in other patients one sees the persistence of the

ideas, but without their sting and engendered hostility.

Apart from this there are a surprising number of useful manipulations of the elderly patient which can be undertaken in hospital. Stimulatory drugs such as amphetamine are sometimes useful, as well as insulin to improve metabolism; vitamin and glucose preparations in debilitated patients are most valuable. It is highly gratifying to see immediate, far-reaching change for the better in an elderly, depressed, retarded patient whose main illness is not primarily affective but secondary to debilitation. Effective metabolic treatment of these patients restores them within a few days to a state of activity they have not enjoyed for many years.

The first principle of care is to free the patient from pain, whether mental or physical. It is surprising how often pain may be present to a degree unsuspected by the doctors and nurses. This is particularly true of mental pain, under which heading I include depression, agitation or anxiety, very often in combination with confusion. The treatment of mental pain is a matter first of diagnosis, next of explanation, and third of appropriate medication. There are few psychiatric conditions of this kind which will not yield, at least to some extent, to medication.

The next problem is that of interest and occupation. Some patients are quite content with a mere existence; they ask nothing more than to pass the time as pleasantly as they can. I think there is a danger that an energetic young person may be over-enthusiastic in activating such patients, under the mistaken impression that they cannot be enjoying themselves unless they are active or creative. This in my opinion is to mistake rehabilitation for management. At the same time there are many others who are distressed by inactivity, and particularly by any feeling of uselessness. For those patients it is worth a great effort to give them something they can make or, if they belong to a higher level of society, something they can administer or organize. If an interest can be found, it is astonishing to see the energy which such patients can profitably release.

A third group of patients are those with phobias, anxieties, and compulsions to which they may have fallen a prey, with the loss of mental control due to the ageing process. This group is very difficult to manage, for they are usually so preoccupied with themselves that they cannot be persuaded to take part in any communal activity. Rather heavy sedation is usually necessary, and it is advisable to choose a nurse who will have a great deal of patience and be ready to accept a very small reward in return. It is, however, a mistake to leave these patients on their own if it can possibly be avoided, because they nearly always degenerate further under such circumstances, and moreover, have an unsettling effect on those about them.

There remain the group whose minds have failed to such an extent that it is kinder to keep them at as low a mental ebb as possible. These are usually people who have lived active, useful lives until the time of their illnesses. Very often they are much above the normal in initiative and intelligence. They find themselves in the terrible position of being unable to use their minds adequately, and yet sufficiently aware to know of their predicament. No form of medical treatment is really satisfactory for them. Attempts to stimulate the mind are nearly always a failure because such treatment is, in common language, flogging a dying horse. I think it is better to use really adequate doses of the tranquillizing and sedative drugs for such patients, and to take enough time to explain carefully to the relatives the need for what must appear to them to be the extinction of the personality they used to know.

I have stressed the need to avoid over-stimulation of the aged person, though I do not suggest that we should go back to early mental hospital days when sedation of certain patients to a stage of apathy was regarded with satisfaction. I am rather advising caution in applying to elderly patients the urge to rehabilitation which developed during the war. There are nevertheless many aged people who have one or two remaining interests. Provided the doctor and his co-workers take enough time to find out these interests, and they do not impose too great a strain on the patient, much can be done with them in a suitable community. It is of course far less easy to produce the appropriate activity in the patient's own home without the stimulus of common life with his fellows. Even if the patient has no very active interest he may sometimes be much entertained by sensory stimulation. Many years ago, Ranchin, of Montpellier, recommended music and singing, and this part of his advice can be followed with profit. To-day we can add visual enjoyment by television.

I would like to add a final word about this problem of activity and entertainment. One of my patients, who was very fond of his pint was urged by me to broaden his interests and even take a little exercise every now and again. To this he replied "I appreciate your advice, doctor. It must be wonderful to know so much about health—but I think you will agree with me that as you look round you will see more old drunkards than old doctors."

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Section of Neurology

President—DENIS BRINTON, D.M.

Meeting
November 5, 1959

MEETING AT THE NATIONAL HOSPITAL FOR NERVOUS DISEASES, QUEEN SQUARE, LONDON

THE following cases were shown:

? Vogt-Koyanagi Syndrome.—Dr. F. CLIFFORD ROSE (for Dr. DENIS WILLIAMS).

Three Cases of Familial Swelling of Optic Discs with Visual Failure.—Dr. K. J. ZILKHA (for Dr. J. St.C. ELKINGTON).

Raeder's Syndrome (Paratrigeminal Paralysis of the Ocular Sympathetic).—Dr. J. B. FOSTER (for Dr. J. MARSHALL).

Glioma of the Optic Chiasm.—Dr. R. BROWN (for Mr. HARVEY JACKSON).

Hyperostosis Frontalis Interna.—Dr. K. L. GRANVILLE-GROSSMAN (for Dr. W. GOODDY and Dr. D. EDWARDS).

Collagen Disease with Myelopathy.—Dr. G. S. WAKEFIELD (for Dr. J. MARSHALL).

Spinal Schistosomiasis.—Dr. J. D. CARROLL (for Dr. J. MARSHALL).

External Carotid Angioma.—Dr. D. G. POTTS (for Dr. J. W. D. BULL and Dr. DENIS BRINTON).

Meeting
December 3, 1959

THE NEUROLOGICAL COMPLICATIONS OF DIABETES

Neurological Complications of Diabetes Mellitus: Clinical Aspects

By HUGH GARLAND, T.D., M.D., F.R.C.P.

Leeds

Introduction.—According to the Papyrus Ebers, diabetes was known about 3,500 years ago, in the days of Moses, but the neurological complications were probably not recognized until 1864 (Goodman *et al.*, 1953; Joslin *et al.*, 1959) when it was concluded that diabetes itself was neurogenic, though this idea was soon abandoned.

In 1959 the total picture of the neural complications of diabetes is confused and the many publications are contradictory. There may be several reasons for this confusion. Diabetes appears to be a very common disease in all races, and it has been estimated that there are 3 million diabetic patients in the United States (Joslin *et al.*, 1959). In Great Britain there has been no extensive survey of the problem, but a careful study of a small community (Walker, 1959*a*, *b*) has shown an incidence of about 1·3% in the population, and if this were true of the whole of Great Britain there would be about 650,000 such cases. The prevalence of neurological complications has been estimated at every figure from none to nearly 100% (Goodman *et al.*, 1953), but the general view is that about 60% of diabetics have such complications, which means about 400,000 in Great Britain. This must be compared with an estimated incidence of about 30,000 examples of Parkinsonism or disseminated sclerosis at any given time (Garland, 1952), and I think any clinical neurologist would find this high figure difficult to accept. Further, if the incidence of neurological complications of diabetes is 60% or more it would seem that these syndromes are not really complications but are part of the total picture of diabetes, and perhaps as frequent as polyuria, polydipsia, or loss of weight. Before discussing the reasons for the very variable incidence claimed we must first approach the problem of terminology, which in this context (as is equally true of epilepsy or head injury) is now inadequate and often inaccurate. In the earlier writings most of the neurological accompaniments of diabetes seem to be included under the titles of polyneuritis or peripheral neuritis. In the next phase the term diabetic neuropathy was introduced, and clearly some workers, both past and present, have used this term to cover all neural involvement at any anatomical level (Goodman *et al.*, 1953). By comparison with the terms encephalopathy, myelopathy, and myopathy, the use of "neuropathy" should be restricted to lesions of peripheral nerves. But here difficulties arise immediately; if the nerve roots are included as

part of the peripheral nerve then neuropathy must include lesions of posterior root ganglia, and if the sensory ganglion cells are to be included why not the motor? If motor or sensory ganglion damage is to be called neuronopathy this term will have to be qualified by the appropriate functions. If diabetic coma is excluded there seems to be no diabetic encephalopathy, either acute or chronic, and the incidence of strokes is probably not higher in diabetics than others, when allowance is made for age and hypertension (Joslin *et al.*, 1959). No acute form of diabetic myelopathy is known.

Some authors include as neurological complications of diabetes a variety of symptoms without physical signs—of which the commonest is pain—and it may be that such symptoms, which are easily reversed by diabetic control, are essentially neurogenic, but this is not proved. Others have added various isolated nerve palsies—I think incorrectly—though these have never been claimed to be frequent, and in the past decade repeated references have been made to signs and symptoms said to result from diabetic degeneration in autonomic nerve fibres, with or without involvement of medullated fibres. It is often impossible to tell from the name either of the author or of the journal whether published material is neurologically valid.

Nearly all diabetics are under the care of general physicians, and many attend a diabetic clinic. Because such physicians often have no neurological training and little interest in neurology, they may, and do, overlook neurological abnormalities in the diabetic, or, having found them, they may rightly label them as complications or wrongly attribute them to some other nosology.

Muscle and nerve biopsies have been made over the years but the histological interpretation is likely to have been inaccurate in the past. Moreover the important methylene-blue vital staining technique for end-plates was only discovered seven or eight years ago and is not applicable to post-mortem studies. When changes are found in peripheral biopsy material we know nothing of what is happening in the ganglion cells at the same time. Although diabetic damage may affect the whole neuron it has been suggested, on the basis of histology of biopsy specimens (Woolf and Malins, 1957), that there is a "dying-back" process starting in the end-organ, which would explain why symptoms usually start in the periphery. Unfortunately very few post-mortem studies seem to have been made of diabetics with neurological abnormalities, but in one very important report (Bosanquet and Henson, 1957) extensive degeneration in central and peripheral sensory pathways was thought to have started probably in root ganglion cells; although this patient was 70 there was little histological evidence of arterial disease. Finally, it is generally agreed that most neurological syndromes are reversible and therefore they are rarely available for post-mortem study. For these and probably other reasons our knowledge is still sketchy and contradictory.

Clinical Syndromes, Terminology and Ætiology

Diabetic sensory neuropathy.—Much the commonest neurological complication of diabetes is a purely sensory syndrome, comprising pain in the legs (often only nocturnal), muscle tenderness, loss of ankle-jerks, and loss of vibration sense in the feet and ankles. The signs and symptoms tend to spread upwards, other sensory modalities are involved later, and sometimes the arms may be affected. The syndrome is almost invariably bilateral and symmetrical, and commoner in the second half of life, often (but by no means always) being seen in diabetics of long standing who have not been under full diabetic control. Despite a long history of poorly controlled glycosuria, diabetes in these patients is often mild (Rundles, 1945). Perhaps the earliest sign of this syndrome is loss of vibration sense which is so slight that it can only be detected electrically. I have already mentioned that pain may occur without physical signs, and the converse is equally true. Sometimes there is a fairly close clinical resemblance to tabes dorsalis, and Argyll Robertson pupils have been described, though it has been suggested that this pupillary anomaly has never been demonstrated by a neurologist (Martin, 1953*a*). One of the difficulties in assessing the frequency of sensory neuropathy is that identical signs and symptoms are often found in elderly non-diabetics (Critchley, 1931). In the early stages the diabetic syndrome is easily and rapidly reversible by full diabetic control, and this is perhaps the only important contribution to knowledge in about a hundred years. As already pointed out the anatomical level of the earliest lesions of the syndrome is by no means certain, but since nobody has suggested that they are within the spinal cord I can see no objection to the term diabetic sensory neuropathy, and indeed I cannot suggest a more appropriate title.

Diabetic amyotrophy.—In a series of papers since 1953 (Garland and Taverner, 1953; Garland, 1955, 1957) I have described a purely motor diabetic syndrome. At first I thought this was a new clinical discovery, but it was in fact a re-discovery of an old and forgotten observation. Originally I regarded this as a

diabetic myelopathy on the basis of the distribution of muscle weakness, electromyographic changes, and the presence of extensor plantar responses. But I later found that the plantar response is often flexor, and in the absence of post-mortem confirmation I felt that the syndrome was better described as diabetic amyotrophy, since of all the manifestations weakness and wasting of muscles are the only constant features. That this is in some way determined by diabetes seems to be generally accepted. I have now seen 30 examples of this condition. The reactions of others to my first papers varied; many thought that this was only a product of my Leeds imagination but most neurologists soon found one or more examples, and recently 12 have been recorded in Zürich (Bischoff, 1959) and others in Boston (Sullivan, 1958).

Apart from being a purely motor syndrome this condition shows many differences from diabetic sensory neuropathy. The signs and symptoms are almost invariably asymmetrical, and often almost unilateral. As with the sensory form the legs are always affected first, and indeed the arms are rarely involved, but the proximal muscles tend to be most involved. Fasciculation is seen occasionally. The appropriate tendon-jerks are depressed or absent, and the plantar responses are sometimes extensor. Pain is usual, always being felt in the region of the affected muscles; in one example of mine the pain was abdominal and related to changes in the rectus abdominis. The protein content of the spinal fluid is sometimes considerably raised, as in sensory neuropathy. The history of diabetes is usually short and occasionally amyotrophy is the presenting symptom, but this is not always true and I have seen amyotrophy suddenly complicate diabetes of over twenty years' duration. Amyotrophy usually appears in the less severe examples of diabetes and no patient of mine has previously been in diabetic coma. The syndrome is known to relapse, and recovery from amyotrophy may be followed by sensory neuropathy (Sullivan, 1958). In my experience this syndrome is totally reversible, though muscle atrophy and electromyographic changes may be the last features to return to normal. The only treatment necessary is full diabetic control, and for this I think a desirable though arbitrary figure for the blood sugar two hours after a meal is 150 mg%. I am not prepared to defend myself on this point if attacked by a diabetician, but I am satisfied that such control will prove adequate, although the use of the insulins is almost invariably essential. In establishing a diagnosis of diabetes I have always relied on the glucose tolerance test, and I have sometimes accepted as evidence abnormally high levels (over 200 mg%) in a "lag" curve after a normal fasting level; some will no doubt say this is not diabetes, and I may have to change the nomenclature to hyperglycæmic amyotrophy.

The differential diagnosis of diabetic amyotrophy lies largely in laboratory tests. The imitators are polyarteritis nodosa, syphilitic amyotrophy, hypoglycæmic amyotrophy, or motor neuron disease in those examples that are painless. The majority of my cases had previously been given an incorrect neurological label—usually either sciatica or motor neuron disease—but I have not seen these errors committed by a neurologist, although before 1953 we must all have overlooked this condition.

The underlying pathology of diabetic amyotrophy has not yet been established, and the scanty evidence is conflicting. In one recorded example, in which I would accept the diagnostic criteria (Alderman, 1939), post-mortem studies showed gross changes in anterior horn cells, with appropriate asymmetry and little else. In the only post-mortem study made in Leeds (Harriman, 1959), where again I would accept the diagnostic criteria, virtually no histological changes were seen in the spinal cord or nerves though the muscles showed striking changes, apparently of neurogenic atrophy. This observation raises the possibility of a purely biochemical neural lesion, at any anatomical level, which, though not producing neurohistological change would, at any rate in its early stages, disturb function sufficiently to produce serious disability and even secondary histological changes in muscle. But this theory would not conform with the previously described changes starting in end-plates. At the moment, therefore, we must accept the entity of reversible diabetic amyotrophy, with the possibility of a lesion at any point from anterior horn cells to muscle end-plates, or at several levels, and with clinical and electrical evidence that the spinal cord is sometimes involved even without histological change.

Mixed sensory and motor diabetic syndromes.—It has always been recognized that diabetic polyneuritis, though largely sensory, might from time to time show minimal motor involvement. I have never seen, or heard of, a florid example of diabetic sensory neuropathy in combination with diabetic amyotrophy, and it may be that for some ætiological difference these syndromes have only the common denominator of diabetes. But even though the syndrome appears to be purely sensory on clinical grounds biopsy study may still show changes in motor end-plates

(Harriman, 1959). The clinical picture of diabetic sensory neuropathy is usually very different from that of other forms of polyneuropathy and rarely has to be considered in the differential diagnosis of "polyneuritis", except when the latter is carcinomatous.

Diabetic autonomic syndromes.—Involvement of the autonomic nervous system in diabetic degeneration has had frequent reference in the past ten years (Metcalfe, 1949; Martin, 1953*b*; Keen, 1959) though similar suggestions had been made long before this. If true, this group of signs and symptoms is extensive, and not very generally recognized—certainly not by myself. Many disabilities are said to result from diabetes and, in particular, from diabetic degeneration in the autonomic system, whether or not diabetic sensory neuropathy is associated. One of the commonest is paroxysmal diarrhœa, which is usually nocturnal, with very frequent fluid stools, and sometimes with fæcal incontinence. Impotence may appear as an isolated symptom—which may mean failure of erection, loss of libido, or failure of ejaculation (more properly then termed sterility). Paralysis of the bladder, with loss of sensation and a sizeable amount of residual urine, and even retention, may occur without peripheral sensory loss, but often in association with impotence. Other signs and symptoms include loss of sweating (usually in anæsthetic areas), postural hypotension, postural tachycardia, neuropathic joints (especially in the feet), perforating ulcers, possibly pupil changes, and even gastric retention. Dependent œdema without cardiac or renal cause has always been known to accompany peripheral neuritis on occasions, and is also said to result from autonomic degeneration. Impotence is said to occur in 75% of male diabetics between the ages of 60 and 65 (Keen, 1959), though without a control series this figure is not impressive; more important is the incidence of impotence in 25% of diabetics between the ages of 30 and 35. An assessment of the precise relation between nocturnal diarrhœa and any neurological accompaniments of diabetes is very difficult, because the diarrhœa is paroxysmal and is said to have been reversed by the use of antibiotics (Keen, 1959). But it is claimed that most of these autonomic disturbances can be reversed by diabetic control, though impotence may only be relieved if it be of fairly recent and sudden onset. I have not seen any of these symptoms in combination with diabetic amyotrophy.

It is suggested that non-myelinated nerve fibres are the first to suffer in diabetes (Martin, 1953*b*), and that perception of pain and extremes of temperature, as well as tendon areflexia, may all be determined by non-myelinated afferent pathways. These views are of importance in regard to ætiology in general, because it seems that non-myelinated fibres are less vulnerable to ischæmia than the larger myelinated fibres, suggesting that diabetic degeneration is more likely to be determined by metabolic than ischæmic changes.

It may be pertinent to draw an analogy with the known sequelæ of extensive sympathectomy, which has been done in many patients who have now been under observation for years. Postural hypotension is a well-known sequel, but retention of urine, nocturnal diarrhœa, neurogenic arthropathy, and perforating ulcer have not been seen. Sweating is never totally and permanently abolished after sympathectomy, except below the knees, and though impotence in all its forms often results it is by no means a certain hazard (Shucksmith, 1959). We can only conclude that diabetic involvement of the autonomic nervous system presents formidable and at present insoluble problems. This has always been true of all autonomic disorders, and our lack of knowledge is not helped by the variable behaviour of the autonomic system in experimental animals.

Cranial and other isolated nerve palsies.—Diabetes has often been claimed as the cause of palsies of isolated peripheral nerves, and particularly the oculomotor nerves. The largest number of diabetic ocular palsies seen by one observer seems to be 30 (Collier, 1930); in this series the VI nerve was most frequently affected but all three oculomotor nerves were sometimes involved on one or both sides. All these patients were in the second half of life, and all the ocular palsies recovered. I find it very difficult to accept this hypothesis especially as there was no reference to blood sugar studies or details of treatment. Sudden ocular palsies frequently appear in non-diabetics in middle and old age, and these usually make a complete recovery; their precise ætiology has always been a matter for speculation, but there has been one very important study of a III nerve palsy, in a diabetic, in whom opportunity for post-mortem study arose (Dreyfus *et al.*, 1957). A sizeable fusiform swelling of the nerve was found in its intracavernous course, and histological studies suggested that the essential lesion was occlusion of one of the vasa nervorum. Such occlusion was not identified but this might have been the result of damage at the time of removal of the brain. It was admitted that the diabetes might well have been fortuitous. However, this theory stimulated interest in the blood supply of the III nerve, about which little was previously known. Although the blood supply of the distal and

proximal parts of the III nerve was established in a series of post-mortem studies, that of the intra-cavernous portion eluded demonstration.

Other cranial nerve palsies, especially of the VII, have been ascribed to diabetes, and so have palsies of isolated nerves in the limbs; these are said to have a sudden onset and to be irreversible (Collier, 1930). I have never seen these myself, and I doubt their validity (cf. Goodman *et al.*, 1953). I am prepared to concede that bizarre areas of anæsthesia, with no acceptable anatomical substratum, may be evidence of diabetic sensory neuropathy, but in assessing any neurological syndrome it must always be remembered that diabetes is common, and that the association with neurological syndromes may be accidental.

Ætiology of the diabetic neurological syndromes.—Three explanations for the neurological complications of diabetes have been advanced in the past—namely, vitamin deficiency, hyperglycæmia or some intermediate disturbance of metabolism, and ischæmia resulting from arterial changes consequent on or aggravated by diabetes. There is little support for the first concept (Martin, 1953*a*; Keen, 1959), but the other two are intertwined and the evidence is more than contradictory. It has often been suggested that peripheral neuropathy in diabetes is determined by vascular occlusion from atheroma or medial thickening at various arterial levels, which is proved to operate in the neuropathy of polyarteritis nodosa. Against this theory are the facts that many such diabetics show no clinical evidence of arteriopathy or hypertension, that the neurological syndromes are totally reversible by diabetic control alone, and that these syndromes are often absent in gross arteriopaths whether or not they be diabetics. Certainly such a concept would not be acceptable when the lesion is in the spinal cord, since spinal arteriosclerotic syndromes do not seem to exist—which is very remarkable in view of the frequency of cerebral arteriosclerotic disorders. Of recent years an attempt has been made to establish the entity of a specific diabetic angiopathy, which is reversible by diabetic control. This theory turns largely on the application of special staining techniques to nerve biopsy material, and a case seems to have been established, though further study is required (Fagerberg, 1959).

The same basic pathology has been ascribed to the neurological, retinal, and renal complications of diabetes, and they are said to be clinically associated. Diabetic gangrene, retinopathy and probably nephropathy are thought to have a vascular rather than a primarily metabolic basis, and it is now suggested that this may be a specific diabetic angiopathy. The frequent association of sensory neuropathy, retinopathy, and nephropathy may be established (Joslin *et al.*, 1959), but I have not encountered diabetic amyotrophy in association with retinal or renal lesions, although diabetic angiopathy has been claimed as the basis of this amyotrophy (Sullivan, 1958). It is a curious fact that the microaneurysm which is so characteristic of diabetic retinopathy has not been seen in any other organ, except perhaps the kidney (Ashton, 1959).

All we can say to-day is that on the basis of histological studies there are those who think the neurological complications of diabetes are usually determined by arterial disease (Woltman and Wilder, 1929) or even by a specific diabetic angiopathy (Sullivan, 1958; Fagerberg, 1959), and those who advance cogent arguments against such theories (Rundles, 1945; Martin, 1953*a*; Bischoff, 1959). There is therefore no agreement as to whether the important factor is metabolic or ischæmic, nor do we know the anatomical level of the early lesions, and for this reason anatomical terms are better withheld from diagnostic labels.

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The Anatomical and Functional Aspects of the Neurological Lesions of Diabetes

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IN this paper I shall try to interpret diabetic neuropathy in terms of disturbed function.

What are the facts that we have to explain? First, I think there is no doubt that in most cases we are dealing with a lesion of the peripheral nerves: all the physical signs point that way, and Woltman and Wilder (1929) found that any lesions in the central nervous system were too slight and inconstant to account for the signs. On the other hand, they, Martin (1953*b*) and Fagerberg (1959) have found degenerative changes and disappearance of axons and myelin sheaths in the peripheral nerves. Our question then resolves itself into the problems: which nerves are affected, where, and by what agent?

As Dr. Garland has shown, the clinical manifestations in diabetic neuropathy show that every kind of peripheral nerve may lose its function—motor, sensory and autonomic. But in general the early and predominant involvement is of autonomic and sensory nerves.

I have been unable to find detailed accounts of the order of loss of the various kinds of sensation in diabetes. Most accounts indicate that touch and pain are lost more or less equally and contemporaneously, though perhaps not so early as the tendon reflexes. Vibration sense and sense of position seem to be lost later, although there are few really detailed accounts (Martin, 1953*a*; Rundles, 1945); temperature sense is rarely mentioned in case reports or papers. Martin found that the histamine "flare", which Lewis (1927) showed to be an arteriolar dilatation mediated through an axon reflex of the posterior root system, is also reduced in diabetes. Bárány and Cooper (1957) found that the flare was lost or reduced in much the same distribution as the loss of sweating.

Workers in my department have been more concerned with the nature of the lesion of the autonomic nerves. Though lesions of these nerves were postulated in 1890, their modern investigation starts with Rundles, who in 1945 reviewed 125 cases of diabetic neuropathy, 35 investigated personally. He noted disturbances of gastrointestinal tract, e.g. diarrhœa, and of the genito-urinary tract, e.g. retention of urine and impotence, in association with vasomotor and sudomotor disturbances and occasionally with failure of postural maintenance of arterial pressure; all of which he attributed to disturbances of the autonomic system. Martin (1953*b*) extended Rundles' observations. He demonstrated that in patients with diabetic neuropathy, reflex vasoconstriction to cold and reflex vasodilatation to heat occurred normally in the upper, but were absent in the lower, limbs. This absence was not due to vascular occlusion since tolazoline produced a normal vasodilator response in the feet. These observations were confirmed by Snell (1959).

Bárány and Cooper (1957) investigated in some detail the disturbance of sweating in 9 diabetics. Loss or impairment of sweating was most pronounced at the extremities of the limbs. In the areas of disturbance, faradic stimulation of the skin produced either no, or a reduced area of sweating and of goose skin. Since Lewis and Landis (1930) had shown that the spread of the pilomotor and sudomotor response of the skin to faradism is dependent on the integrity of the postganglionic sympathetic fibres, we may conclude that the lesion of the sympathetic nerves is in the postganglionic fibres. Bárány and Cooper (1956, 1957) also demonstrated a reduction in the areas of sweating and goose skin produced by introducing acetylcholine into the skin, which indicates a similar lesion, as did their finding that goose skin induced by iontophoresis of noradrenaline was prolonged. While there is insufficient evidence to admit of a general statement, there is no doubt that in some patients, e.g. Case I of Keen (1959), the sympathetic disturbance is much more extensive than that of sensation.

In 1931 Lewis, Rothschild and I investigated the paralysis developing in the upper limb in response to ischæmia. We found touch and sense of position were lost early and that temperature and pain and pilomotor activity were maintained longer. Motor loss occurred early. We suggested that this differential paralysis was due to the earlier involvement of the large, fast conducting fibres as described in experiments on the nerves of the cat by Gasser and Erlanger (1929). These observations were extended and confirmed by Lewis and Pochin (1937, 1938), who noted that defects of touch, cold sense, warm sense and fast-conducted pain begin almost simultaneously. They noted the curious association of hypoæsthesia and hyperalgesia, which is also a common finding in diabetic and other neuropathies. And they noted some inconsistencies between their findings and the theory relating them solely to fibre size.

The converse of ischæmia is provided by

cocaine which, as Gasser (1934) showed, paralyses the small slowly conducting fibres first and the large fibres last; pain and the vasomotor nerves are paralysed early, touch later. A somewhat intermediate position is occupied by cooling, which picks out the cold, motor and vasomotor fibres early, touch second and pain and warmth last (Bickford, 1939).

These patterns of differential paralysis of nerves undoubtedly represent physicochemical differences in the nerve fibres themselves, and this irrespective of whether the differential paralysis is a manifestation of fibre size, or of their frequencies and patterns of impulses, which some believe to represent the way in which different modalities are conducted (for review *see* Sinclair, 1955).

I am not aware of any observations on diabetic neuropathy that are sufficiently searching to enable a conclusion to be drawn as to whether the loss of function corresponds closely to any of these three patterns or is different. However, the relatively early and severe lesions in post-ganglionic fibres seem quite unlike the pattern found in ischæmia; and of course there is no doubt that the postganglionic fibres are small and unmyelinated.

The chief interest of diabetic neuropathy to me lies in its meaning. All observers are agreed that there is a correlation between the nervous lesions, those of the retina so recently and admirably reviewed by Ashton (1959), and the Kimmelstiel-Wilson lesion of the kidney. While it is probable that they represent three separate manifestations of one and the same biochemical fault, we may, for the purposes of this discussion, restrict our attention to the nervous lesion. Woltman and Wilder (1929) believed that neither glycosuria nor acidosis played a direct part; nor did infection. They therefore considered the lesions were due to atherosclerosis affecting the blood supply of the nerve trunks. While Rundles (1945) noted that neuropathy was particularly prone to develop in patients whose diabetes was poorly controlled, 56% of his patients had never had coma, acidosis or ketosis so far as could be ascertained. Fagerberg (1959) has recently shown the frequency of deposits of PAS-staining material in the arteries of the sural nerve in diabetes, and again argues the case for ischæmia. However, two arguments make this improbable. In the first place, as Martin (1953*b*) showed, the blood supply to the affected limb is in many cases good. In the second place, as I have shown above, the pattern of loss of function is quite unlike that of ischæmia.

I would like, therefore, to suggest that the lesion of the peripheral nerves is one of the manifestations of the basic biochemical fault that underlies a certain type of diabetes. It is not impossible that this biochemical fault is the manifestation of a single gene, though the evidence is quite inconclusive. But it seems to me possible that if we could define more accurately the biochemical fault in diabetic neuropathy, we might obtain a new approach to the nature of at least one form of diabetes.

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Pyruvate Metabolism in Diabetic Neuropathy

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Knowledge of the biochemical changes that accompany different forms of peripheral neuropathy is still very limited. One biochemical lesion, however, that has been shown to exist in certain types of polyneuritis is a disorder of pyruvate metabolism, and because of these limitations in our knowledge, this communication is mainly concerned with pyruvate metabolism in diabetic neuropathy.

It must be made clear, however, at the outset that although the studies which we have carried out have provided results of interest to the wider problems of diabetes mellitus, they have not as yet produced any positive evidence on which we

can build any theory to account for the development of diabetic neuropathy. They have, however, served to exclude certain possibilities, and suggest perhaps a re-directing of our thoughts, and it is for this latter reason that we have thought it worth while to describe them briefly here.

The clinical similarity that exists between certain cases of diabetic neuropathy and the polyneuritis associated with thiamine deficiency led, as is well known, to the suggestion that this peripheral neurological complication of diabetes might be the outcome of a co-existing deficiency of vitamin B_1.

In order to test this hypothesis Goodhart and Sinclair in 1940 estimated the level of thiamine in the blood, in the form of its pyrophosphate ester which can be regarded as the active derivative of thiamine, in 5 patients with diabetic neuropathy. In 4 out of the 5 patients they found normal levels. The 5th patient, in whom a low level was found, was also an alcoholic, which could of course account by itself for the decreased thiamine level.

Studies were also made, between 1940 and 1943, of the urinary excretion of thiamine before and after a test dose of the vitamin in diabetic patients, with and without signs of peripheral neuritis, and again in the vast majority of cases the values found were within the normal range (Robinson *et al.*, 1940; Pollack *et al.*, 1941; Needles, 1943).

Despite these findings, however, several observers claimed that clinical improvement occurred in patients with diabetic neuropathy following the administration of the vitamin (Fein *et al.*, 1940; Rudy and Epstein, 1945), although other subsequent investigators found that even massive doses of thiamine given intramuscularly failed to produce any improvement (Rundles, 1945; Martin, 1953).

There is therefore no clear or even adequate evidence to support the suggestion that diabetic neuropathy is in the main due to an accompanying thiamine deficiency.

It is, however, now known that the underlying biochemical lesion in thiamine deficiency, namely a block in the normal oxidative pathway of pyruvate metabolism inside the cells, can be produced by a variety of causes other than thiamine deficiency. Further, it is known that certain of these other causes can also manifest the block in pyruvate metabolism by bringing about the development of a peripheral neuritis closely resembling that due to a thiamine deficiency. For example, arsenical polyneuritis is now known to be associated with an inactivation of certain of the enzyme-coenzyme systems concerned in the oxidation of pyruvate, this inactivation resulting from a chemical interaction between the arsenical compound and certain essential sulphhydryl groups in the enzyme system.

Lesions of this type, resulting in impairment of utilization of pyruvate should theoretically be capable of detection by measuring the blood pyruvate level after a loading dose of glucose which will in part be converted into pyruvate inside the cells of the body; if further metabolism of the pyruvate so formed is impaired, then abnormally high levels of blood pyruvate might be expected to occur.

For example, Joiner, McArdle and Thompson applied such a test in 1950 to a group of 40 cases of polyneuritis of different types, together with a group of 50 control subjects. They found that just over half of the patients with polyneuritis showed high blood pyruvate levels at either 60 or 90 minutes after the dose of glucose. By repeating the test after fourteen days of massive parenteral thiamine therapy they were able to show that only a small proportion of these patients showing high blood pyruvate levels had had their pyruvate metabolism restored to normal by the vitamin therapy. The remaining patients showing high pyruvate levels must therefore have had an impairment of pyruvate metabolism due to some other cause.

In view of the known abnormalities of carbohydrate metabolism in the diabetic patient it seemed therefore to be of particular interest to study the blood pyruvate levels in patients with diabetic neuropathy.

In the earlier series Joiner, McArdle and Thompson had included 4 patients with diabetic neuropathy, and had found that in each of them there was virtually no rise in the pyruvate level following the loading dose of glucose. This was in agreement with the finding of Bueding *et al.* (1942) and others, that diabetic subjects without neuropathy also show little or no rise in the blood pyruvate level following the administration of glucose.

This may be attributable to the fact that the diabetic subject is suffering from a relative insulin deficiency, so that the utilization of the loading dose of glucose will be impaired. The blood pyruvate level will only rise as a result of pyruvate entering the tissue fluids from the cells, and if, owing to insulin lack, the entry of the glucose into the cells is impaired, then only a small amount of pyruvate will be formed inside the cells from the loading dose. In other words, an insufficient amount of the loading dose may be entering the cells to yield sufficient pyruvate to show a rise in the blood level if any block in pyruvate metabolism were present.

If, however, a dose of insulin is given to the

diabetic subject at the same time as the loading dose of glucose is taken, then, if that insulin is effective inside the body, it might be expected to increase the rate of glucose entry into the cells sufficiently to show an abnormal rise of blood pyruvate, should any block to pyruvate utilization exist. We therefore gave 7 units of insulin intravenously, together with the oral glucose, and were able to show that a proportion of diabetic subjects did then show a strikingly abnormal, high rise in the blood pyruvate level (Butterfield and Thompson, 1957); for example, in a recent series we have shown that 18 out of a group of 53 diabetic subjects gave an abnormal rise in the pyruvate level after the administration of glucose and insulin (Butterfield *et al.*, 1959). The highest levels in general appear to be found in those patients who are poorly controlled.

Martin (1953) had earlier studied 8 patients with diabetic neuritis using, not a loading dose of glucose, but an intravenous infusion of pyruvate. In this small series he was not able to find any evidence of abnormal pyruvate metabolism, although he himself appears to have found the results of this approach unsatisfactory on technical grounds.

Furthermore, although alloxan diabetes may present a different and possibly a more complex metabolic picture, there is certainly evidence that in this condition also pyruvate metabolism is defective. Thus, Pearson *et al.* (1949) have shown that cardiac and diaphragm muscle from alloxan-diabetic rats show a diminished ability to convert pyruvate to CO_2, and El Hawary and Thompson (1954) found a significant rise in the blood pyruvate level of alloxan-diabetic rats.

Because of the evidence that now exists of abnormal pyruvate metabolism in at any rate a proportion of diabetic subjects it was decided next to investigate whether there is any correlation between high pyruvate levels and the existence of neuropathy by measuring blood pyruvate levels during glucose-insulin tests.

We have therefore recently carried out these measurements in 18 diabetic patients showing involvement of the peripheral nervous system.

These 18 patients comprised 4 groups:

(1) 12 patients with chronic peripheral neuritis, all showing signs of bilateral sensory and reflex changes, with or without weakness. Patients with absent ankle-jerks or impaired vibration sense without other signs were not included.

(2) 2 patients with acute peripheral neuritis, showing bilateral sensory and reflex changes without weakness: these patients were badly controlled and the symptoms improved rapidly with treatment.

(3) 2 patients with mononeuritis multiplex, the first with a right radial and left lateral popliteal palsy, and the other with a right ulnar and bilateral popliteal lesions.

(4) 2 patients with diabetic amyotrophy (Garland, 1955).

In carrying out the tests, 50 grams of glucose was given by mouth, and 7 units of insulin injected intravenously. Blood was taken at zero time, in the fasting, rested state, and again at 60 minutes after the dose of glucose and insulin, the patient being kept at rest.

Pyruvate was estimated by the method of Friedemann and Haugen (1943). In addition to pyruvic acid, this method will also estimate, to varying degrees, other keto acids including aceto-acetic acid. In studying diabetic patients in particular, it is therefore important to demonstrate that high pyruvate levels, as determined by the Friedemann and Haugen method, are in fact due to pyruvate and not to aceto-acetate. In a series of patients showing particularly high levels, or who were known to be liable to develop ketosis, we have therefore also estimated pyruvic acid by a specific method involving paper chromatographic separation of the pyruvic acid from the other keto acids present in the blood extract (McArdle, 1957). Closely similar values were obtained by the two methods, particularly in the case of the rise in the level after administration of glucose.

Table I shows the mean values obtained in a group of 23 healthy control subjects, in 30 diabetics without neuropathy, and in the 18 diabetics with neuropathy.

TABLE I—MEAN BLOOD PYRUVATE LEVELS IN GLUCOSE-INSULIN TESTS

	No. of subjects	Blood pyruvate (mg/100 ml)		
		Fasting	60 min	Rise at 60 min
Healthy controls	23	0·64 ± 0·03	0·90 ± 0·03	0·26
Diabetics without neuropathy	30	0·94 ± 0·09	1·56 ± 0·16	0·62
Diabetic neuropathy	18	0·90 ± 0·06	1·37 ± 0·15	0·47

Taken as a group it will be seen that there is no evidence that the blood pyruvate levels are higher in the patients with neuropathy than in other diabetics. The fasting levels in the 2 groups are closely similar, although they are distinctly higher than the fasting level in normal subjects but both the 60-minute figure and the rise are actually lower in the patients with neuropathy than in those without neurological signs or symptoms.

6 of the 12 patients with chronic peripheral neuritis showed pyruvate levels above the expected normal range, the other 6 giving normal results. Both the patients with mononeuritis multiplex and both of the amyotrophic subjects gave normal results.

On the other hand the 2 patients with acute peripheral neuritis showed high values. Despite this we hesitate to relate the onset of the neurological symptoms in these 2 cases to the observed defect of pyruvate metabolism, since both patients were badly controlled, with blood sugar levels of over 300 mg/100 ml, and it is in just this type of patient that high pyruvate levels are to be expected even in the absence of neurological complications.

It would seem therefore that high blood pyruvate levels are found no more frequently in diabetics with neuropathy than in other types of diabetic patient. So that, just as there is little real evidence of any association with thiamine deficiency, we must also conclude that there is as yet no clear evidence for regarding diabetic neuropathy as due to any other type of impairment of pyruvate metabolism.

At the same time, we now know that many diabetics have a demonstrable abnormality of pyruvate metabolism, and it should perhaps be pointed out that the methods that we have been using, involving analysis on samples of venous blood from the forearm, are relatively crude for the investigation of chronic and perhaps only slight biochemical changes in nerve cells, and we may have to refine our techniques still more before we can with certainty exclude a defect in oxidative metabolism in nerve cells in diabetic neuropathy.

So far, however, we must admit that biochemical investigations into this condition have yielded little that is of positive help. Knowing, however, the extent to which nerve cells appear to depend on the metabolism of glucose for the provision of energy for their normal functioning, it is perhaps to be expected that signs of abnormal functioning in peripheral nerves might be found in a condition involving subnormal glucose utilization by the peripheral tissues, even though the oxidation of glucose by the central nervous system appears to be largely independent of insulin.

At present, however, we can do little more than theorize on the biochemical level as to why peripheral neuropathy should develop in some patients and not in others.

Is it due, for example, to variations in the efficiency of the intracellular metabolism, at a level higher than pyruvate, of the subnormal amounts of glucose entering the cells, these variations being dependent perhaps on the levels of the necessary enzyme-coenzyme system? The levels of these systems will depend on continued protein synthesis, which would appear to be deranged in diabetes mellitus, and which may be more deranged in some subjects than in others. These levels may again be influenced by the degree of accompanying vascular changes in the nerves.

Another possibility, bearing in mind the known abnormalities in lipid metabolism in diabetes, is that in the diabetic subject there may develop a defect in the synthesis of the relatively large amounts of those particular long-chain fatty acids that are present in the lipids of the nervous system.

It is also possible that the raised blood sugar level may affect nervous excitability, since Feldberg (1944) has shown that concentrations of glucose of 0·2% or over inhibit the synthesis of acetylcholine by nerve tissue.

Finally, we must certainly not exclude the possibility that certain types of human diabetes may be associated with the presence of a circulating alloxan-like substance, derived perhaps from some derangement of purine metabolism. Since alloxan is a powerful SH inhibitor, and since it is known that SH inhibitors can produce neuropathies, the presence of an alloxan-like substance might account not only for β-cell damage, but might also explain why in some patients neuritic symptoms develop at so early a stage in the disease, or may indeed be the presenting features.

All these, of course, are speculations, and it is clear that much more work, and on a much wider front, is needed to explore the complex metabolic abnormalities that certainly exist in this condition.

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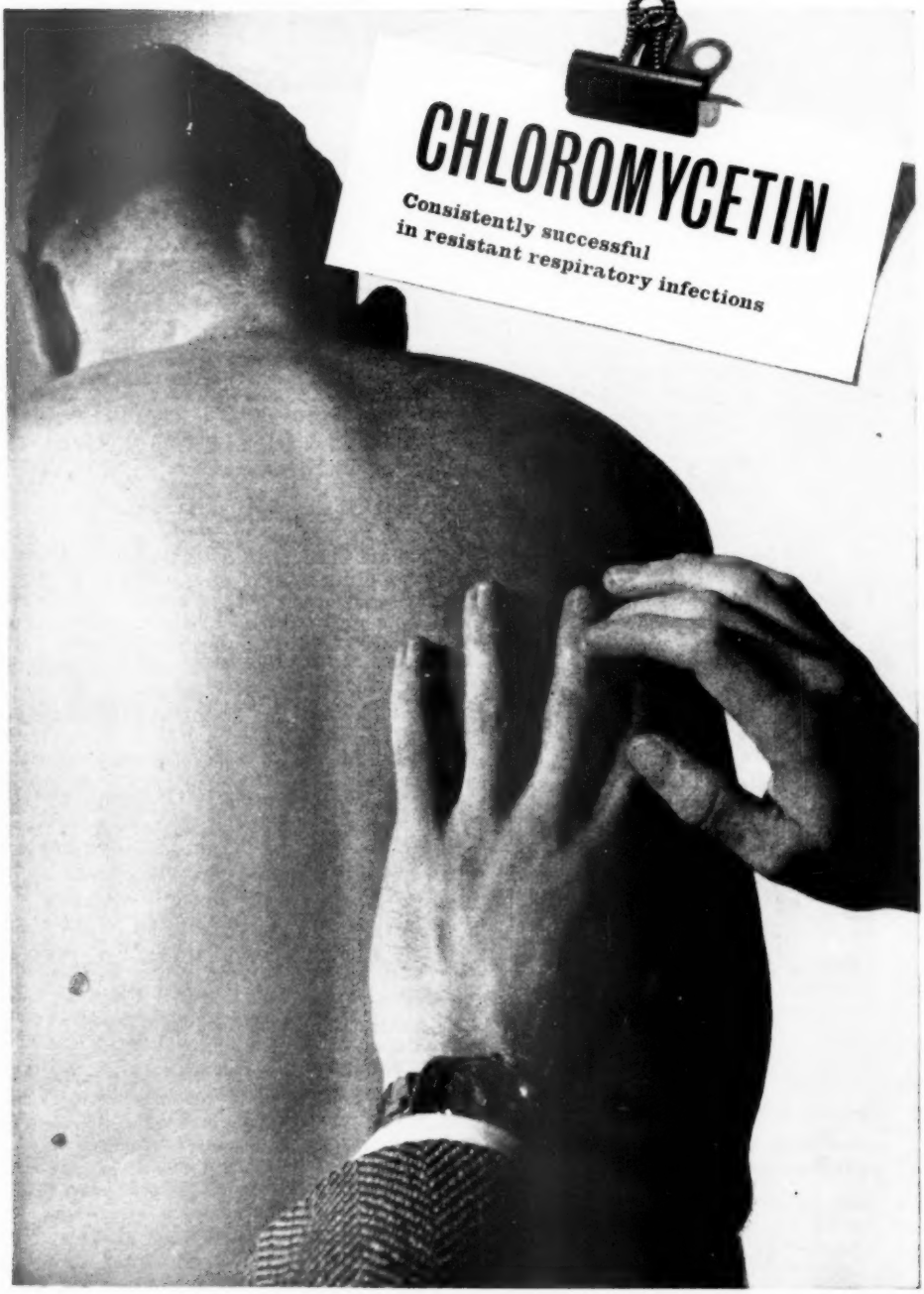

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BOOK REVIEWS

Surgical Aspects of Medicine. Edited by H. Daintree Johnson, M.A., M.B., B.Chir., F.R.C.S. (Pp. xv + 382 + 21; illustrated. 65s.) London: Butterworth & Co. (Publishers) Ltd. 1959.

This book consists of a series of mostly short essays, forty-two in all, on a wide variety of surgical subjects. The editor has written three chapters himself and for the rest has called on thirty-nine other experts in their particular subjects, naturally most of them surgeons. The book aims primarily at providing guidance for physicians and family doctors on when they should consider surgery and what results they may expect. The subjects vary widely, from œsophagitis to hæmorrhoids, from hernia to hypophysectomy, and from painful feet to squint. Readers will find most chapters attractively written with a minimum of lists and classifications. The reviewer liked particularly the article on "the nodular breast" which all doctors and medical students could read with benefit. Both the foreword by Professor Aird and the editor's introduction emphasize the terminological difficulties caused by the same word "medicine" being used both as a comprehensive term for the healing art and also for that part of it practised by physicians.

Napoleon Immortal. The Medical History and Private Life of Napoleon Bonaparte. (Pp. xi + 307; illustrated. 28s.) By James Kemble, Ch.M., F.R.C.S. London: John Murray. 1959.

Q. Another book on Napoleon? Is there anything new in it?

A. Indeed, there is. The author, who has read widely and made many original investigations, discusses from the medical point of view the various illnesses from which Napoleon suffered, and explains how they may have affected his career.

Q. Any surprising views?

A. Yes, evidence is given to show that Napoleon at the age of 40 became the subject of Fröhlich's disease, and the startling suggestion is made that one factor in his defeat at Waterloo was a severe attack of piles from which he was then suffering.

Q. Did you enjoy the book?

A. Yes, for it is written in an easy, sometimes almost colloquial style, and there are many witty (sometimes facetious) asides. Though written in a light style it is a serious contribution to medical and general history.

Progress in Psittacosis Research and Control. Edited by F. R. Beaudette. With a foreword by Richard E. Shope. (Pp. xii + 271; illustrated. $5.0.) New Brunswick, N.J.: Rutgers University Press. 1958.

This book contains the proceedings of a symposium held in 1956 at the New Jersey Agricultural Experiment Station and financed by the Hartz Mountain Products Company.

A large section is concerned with the control of psittacosis in turkeys and certain types of cagebirds using chlortetracycline mixed with the feeding stuffs. There are also contributions on the ecology of the disease in man, birds and mammals and on methods of diagnosis.

Among the contributors are Rene J. Dubos who has written a short but very interesting paper on the factors concerned in converting infection into disease; R. E. Shope on reservoirs of viruses; K. F. Meyer on the disease in parakeets and its control by chemotherapy.

The finding that the disease in parakeets and turkeys can be influenced by feeding foodstuffs containing chlortetracycline in such small amounts as 200 g to a ton of foodstuff is thought by some to provide a practicable method of eliminating or reducing important sources of infection for man.

The possible influence of these findings on public health and quarantine regulations is discussed in a paper by J. M. Andrews of United States Public Health Service.

The book will probably be of greater interest to veterinarians than to medical men but to both it will serve to illustrate current trends in the U.S.A.

Synopsis of Ophthalmology. By William H. Havener, B.A., M.D., M.S.(Ophth.). (Pp. 288; 184 illustrations. 50s.) St. Louis: The C. V. Mosby Company. London: Henry Kimpton. 1959.

This is a concise textbook of ophthalmology covering briefly the diagnosis and management of eye diseases. It is written in an easy style and is profusely illustrated, most of the figures being photographs of patients under the author's care. The book opens with a description of eye examination, followed by chapters on eye injury and the diagnosis and management of the red eye. There follow chapters on medical ophthalmology, neuro-ophthalmology, glaucoma, strabismus, uveitis, degenerative diseases, developmental anomalies, the meaning of eye symptoms, eye-lids, physiology of the eye, ocular therapy, surgery of the eye and preventable blindness.

There is a short glossary and an adequate index. The management of eye diseases is orthodox in outlook, and the book is well balanced.

Blindness in West Africa. By F. C. Rodger, M.D., Ch.M., D.O.M.S. (Pp. xiv + 262; 98 illustrations. £3 10s.) London: H. K. Lewis & Co. Ltd., for the Royal Commonwealth Society for the Blind. 1959.

During 1952–1956 Dr. Rodger covered much of Nigeria and part of Northern Ghana in a survey sponsored by the Royal Commonwealth Society for the Blind. A series of papers have recorded his findings and the present monograph is a most helpful summary and systematization of these studies. Assessed against the incredible difficulties under which this work was carried out one is particularly grateful for so much useful material. It is regrettable that in the discussion on onchocerciasis no indication is given of the significant work of Choyce, which has questioned seriously the role of onchocerciasis as a cause of blindness. It is also unfortunate that the credit for isolating the trachoma virus is not given to the Chinese workers who accomplished this. The monograph as a whole gives an indication of the size of the problem and provides a factual basis for public health and therapeutic measures.

Roxburgh's Common Skin Diseases. Revised by Peter Borrie, M.A., M.D.Cantab., M.R.C.P. London. 11th ed. (Pp. xxiii + 495; illustrated. £1 17s. 6d.) London: H. K. Lewis & Co. Ltd. 1959.

"Roxburgh", which has for long been a favourite with students and general practitioners, has been revised by Dr. Borrie. Its virtues are well known: its readability and the brilliance of the black and white photographs. Although many new paragraphs have been added to bring it up to date and alterations made in certain sections, the book is still too long: there are remnants of past dermatological thinking which could well be discarded. The section on general treatment is the main offender. Is it true, for instance, in 1959, that drugs by mouth have no more than a certain limited value in dermatology? Why is arsenic on one page "rarely used in the treatment of dermatitis herpetiformis" and three pages later it is found reliable in the treatment of that condition? But after the fifty introductory pages the book settles down to sensible and reasonably selective discussion of the commoner diseases. What to leave out and what not to leave out is a problem for every author: it is only too easy for reviewers to put forward their biased suggestions but could not sarcoid have an honourable mention next time? That there will be a demand for another edition, there is no doubt. Let it be hoped that it will be considerably pruned.

The Physiology of Learning. By W. Ritchie Russell, C.B.E., M.D., M.A., D.Sc., F.R.C.P. (Pp. 28. 3s. 6d.) Edinburgh: Royal College of Physicians. 1957.

This is an agreeable addition to the literature which has accrued around the paramount though difficult question as to the nature of learning-processes. Believing that a child's future depends largely on early parental influence, the author is impressed with the lessons now available to educationalists. A strong tradition of customs, loyalties and beliefs plays an important neuro-physiological role in the stable development of an efficient central nervous system. The author believes that these factors are cultivated more successfully in Scotland than in most other countries, though how many others he has experienced we are not told.

The Innervation of Muscle. A Biopsy Study. By C. Coërs, M.D., and A. L. Woolf, M.D. (Pp. xv + 149; illustrated. 42s.) Oxford: Blackwell Scientific Publications. 1959.

In the space of 137 pages the authors describe and depict the variations in the pattern of innervation of the normal muscle and the departures from this in pathology.

Condensed in a generously illustrated and vivid manner, the subject matter is based on the examination of muscle biopsy material stained in various ways. The authors describe their technique and findings and correlate the latter with relevant clinical observations and with the results of other diagnostic methods. The "chambre claire" diagrams with which they supplement some of their photomicrographs go a long way towards facilitating visualization in depth of some of the processes described.

The illustration to text ratio is very high and the authors are to be congratulated not only on the quality of their figures but on the manner in which they have used them to convey so much information with a surprising economy of words.

Those who have had an opportunity of perusing and admiring Dr. Coërs' previous work in French and regretted their linguistic shortcomings will welcome this book by the co-authors.

Pædiatrics for the Practitioner. Supplement 1958. General editors: Wilfrid Gaisford, M.D., M.Sc., F.R.C.P., and Reginald Lightwood, M.D., F.R.C.P., D.P.H. (Pp. v + 140 + 6; illustrated. 35s.) London: Butterworth & Co. (Publishers) Ltd. 1958.

This supplement is divided into two parts, the first containing five original articles and the second being a noter-up which keeps the original volumes completely up to date.

The article on chemotherapy by Wilfrid Gaisford brings sulphonamide and antibiotic therapy up to date and points the way to new uses as we gain a greater understanding of virus disease. He indicates clearly the basic principles of chemotherapy and gives definite direction on dosage.

Julian Katz's short chapter on behaviour disorders makes interesting reading but lacks definite guidance to the practitioner in the methods he may use in tackling the problems that arise. An excellent article on urology by D. Innes Williams describes the scope of his investigations and stresses the importance of a good clinical history and observation of the patient, which will often reduce the number of special investigations required.

Articles on chromatography by C. E. Dent and electroencephalography by W. A. Cobb provide stimulating reading for all enthusiastic doctors. The techniques employed are highly complicated and the interpretation of the results is not yet clear cut, but they have already provided explanations of certain disease processes not known before, and here and there can be used for definite diagnostic procedure.

In Part II, the Noter-up, great care has been taken to cover every chapter in the original three volumes so that they are completely up to date. This is an excellent supplement which fully supports the original three volumes on Pædiatrics.

Arterial Embolism in the Limbs. By A. L. Jacobs, M.A., D.M.(Oxon.), F.R.C.P. (Pp. xii + 200; illustrated. 35s.) Edinburgh and London: E. & S. Livingstone Ltd. 1959.

This book embodies a careful study by a physician of over a hundred incidents of embolism together with a critical review of the whole subject. Most incidents were treated conservatively and it is this material which is most valuable as it gives a background against which the results of active intervention can be assessed. The author finds that spontaneous recovery is almost invariable in brachial or popliteal embolism. Embolism of the larger arteries carries a greater risk to the limb and in these cases embolectomy holds first place in treatment. Even in this group the statistical evidence in favour of surgery is not overwhelming. If cases of embolism in the aorta or in the main sites of lodgement down to and including the superficial femoral are considered, the figures are 50% limb survival with non-intervention compared with 84% in the best surgical series quoted, that of Warren. Other published figures for surgery are little better than those obtainable without operation.

It is often found on the introduction of some new form of surgical treatment that the prognosis in the disease either in its natural course or with medical treatment is unknown. Examples that come to mind include arterial hypertension, portal hypertension, arterial thrombosis and certain cardiac defects. Arterial embolism used to lie in this category but Dr. Jacobs has done much to raise it from it. His book will be of very great value both to surgeons and physicians interested in cardiovascular problems.

A Catalogue of the Portraits and other Paintings, Drawings and Sculpture in the Royal College of Surgeons of England. By William LeFanu. (Pp. xii + 118 + 52 plates; 30s.) Edinburgh and London: E. & S. Livingstone, Ltd. 1960.

Mr. LeFanu's catalogue is a model for the extent and completeness of its information and for its urbane presentation. The descriptions are full and vivid; the provenance of the works of art is given, with notes of published reproductions. There are delightful sidelights on the subjects themselves. It is that rarest of catalogues, one to which one turns not only for specific information but also for the pleasure of browsing. What speculations could not follow the notes on the statuette of the bearded Hijmans van den Bergh that "in later life (he) wore a moustache but no beard"? What may Queen Victoria have said to Thomas Walker "a Crimean casualty": did his jacket ever bear more than "a lance-corporal's stripe": and does one not look at the portrait all the more kindly for knowing that Walker recovered from his trephining? Another happy feature of some of the entries is the note of the opinion of the sitter, or the comment of someone who knew him, on the finished portrait or effigy.

The letterpress is worthy of the standard of the text; the half-tone illustrations, grouped together in one section, are pleasingly arranged, though they appear somewhat over-dark. With

so much richness in the book it is ungracious to cavil about the quality of the four colour plates, the more so as technical difficulties in their preparation, away from the originals, must have been formidable. None the less they do fall below the standard set by the text, both in matter and style.

The Excitable Cortex in Conscious Man. By Wilder Penfield, O.M., C.M.G., Litt.B., M.D., D.Sc., F.R.C.S., Hon. F.R.C.P., F.R.S. (The Sherrington Lectures: V.) (Pp. ix + 42; illustrated. 10s. 6d.) Liverpool: Liverpool University Press. 1958.

The sustained output of serious work from the Montreal Neurological Institute never fails to attract admiring attention. This little monograph constitutes the fifth Sherrington Lecture as delivered by Professor Penfield. The subject matter is familiar and however much the conclusions may be questioned the thoroughness of the work that went into this research must be deemed superlative. For it is only too easy to lapse into criticism—that "recourse of the sterile, designed to demonstrate the intellectual superiority, culture, and omniscience of the critic" as Chevalier said. "It is not uncommon", he went on to proclaim, "for critics to attribute more importance to the fifty lines they write than the three or four hundred pages of the work before them and from which they drew the material for their pretentious dissertation." Penfield's introductory chapter is charming.

The Mammalian Cerebral Cortex. By B. Delisle Burns, B.A.(Cantab.), M.R.C.S., L.R.C.P. Monographs of the Physiological Society, No. 5. (Pp. vii + 120; illustrated. 21s. 0d.) London: Edward Arnold. 1958.

Here is an up-to-date monograph dealing with a topical, important and none too easy subject. It is to be commended on several scores. The author has avoided physiological jargon. Where necessary he has supplied definitions of technical terms. He has cut down arithmetical interpolations to the minimum. There is a judicious interlarding of established fact with the author's own experiences and opinions, and the two sets of data are sharply distinguished. Tabulation and summarizing are adopted freely within the text as an aid to clarity of presentation. The figures are simple and the bibliography usefully full. Chapter 5 which deals with the problems of memory and the nature of learning is particularly good. In all it is a book which can be strongly recommended.

Surgery in World War II. Neurosurgery, Vol. I. Medical Department, United States Army. Editors: R. Glen Spurling, M.D., and Barnes Woodhall, M.D. To be published in 2 vols. (Pp. xix + 466; illustrated. $5.) Washington, D.C.: Office of the Surgeon General, Dept. of the Army. 1958.

The first part of this book deals with the organization which was developed to meet the needs of modern neurosurgery in head trauma. In order to obtain a sufficient number of neurological surgeons, the U.S. Army provided a special short training course for young general surgeons. Thereafter, they were assigned as assistant neurosurgeons to active military units where they acquired the personal experience essential before they could become expert in this rather special field. Dr. Woodhall emphasizes the value of a sound background of general surgery. The comments of Dr. Francis Grant upon certain shortcomings of the theoretical training were refreshingly realistic. A graceful tribute is paid to British military and civilian neurosurgeons for the help they gave in the training of U.S. Army personnel.

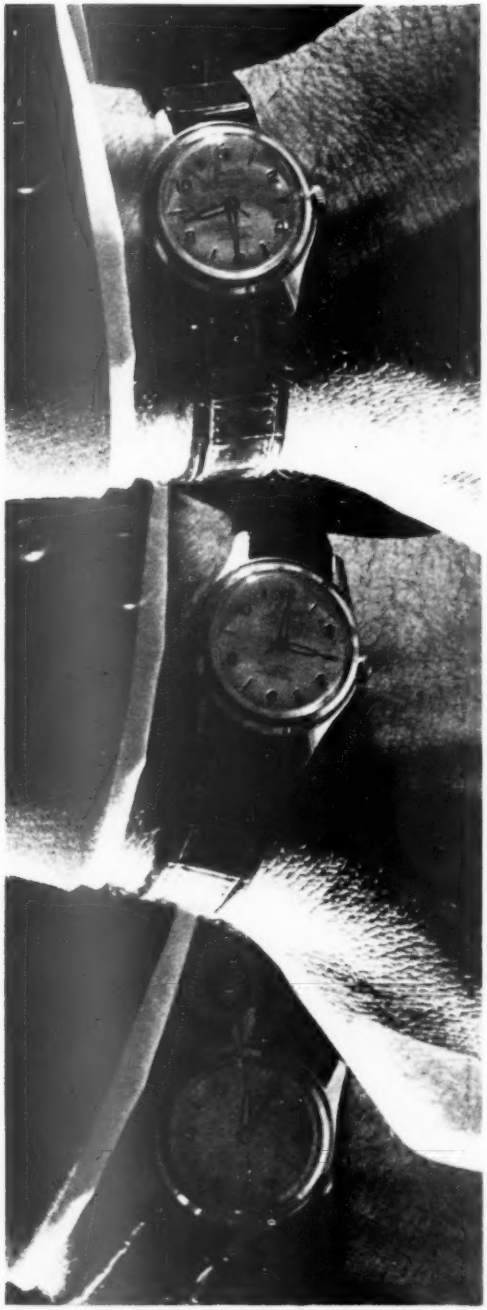
The treatment of craniocerebral injuries in wartime is excellently described. Closure of the dura mater came to be recognized as of major importance. Delayed primary debridement was found to be justified if this brought the casualty to the hands of an expert neurosurgeon. Retained bone fragments were commonly the cause of brain abscess and here a radical attack proved the most successful. Tantalum plate was extensively used for filling defects in the skull and on occasion was found valuable as a method of treating brain fungus which defied other and simpler methods of dressing. The book is well produced, but suffers from a lack of illustration by photographs.

Synopsis of Gynecology. By Robert James Crossen, M.D., Daniel Winston Beacham, M.D., and Woodard Davis Beacham, M.D. 5th edit. (Pp. 340; illustrated. 48s. 6d.) St. Louis: The C. V. Mosby Company. London: Henry Kimpton. 1959.

This is the fifth edition of a work which originally appeared in 1932. In the first edition, the book took the form of a synopsis of Crossen's well-known and classical "Diseases of Women".

In this new edition much material has been added and this little book now contains in small compass an extremely concise and complete survey of gynæcology.

It will appeal to those who want a quick reference to aspects of this specialized subject. The authors have been successful in achieving the right balance between the synoptic style and yet an eminently readable text.



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ATKINSON, J. (1921) J. biol. Chem., 47, 134.

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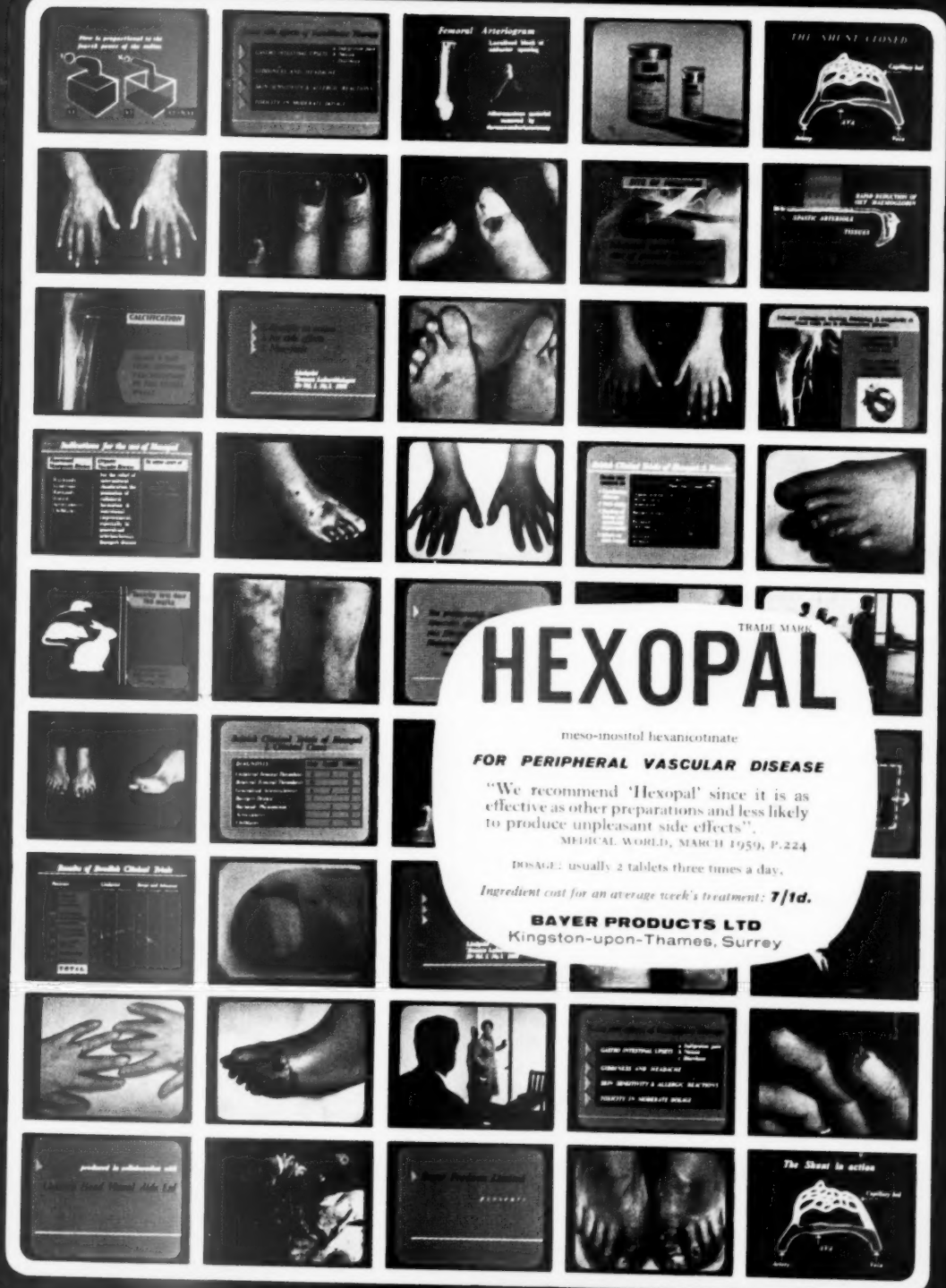

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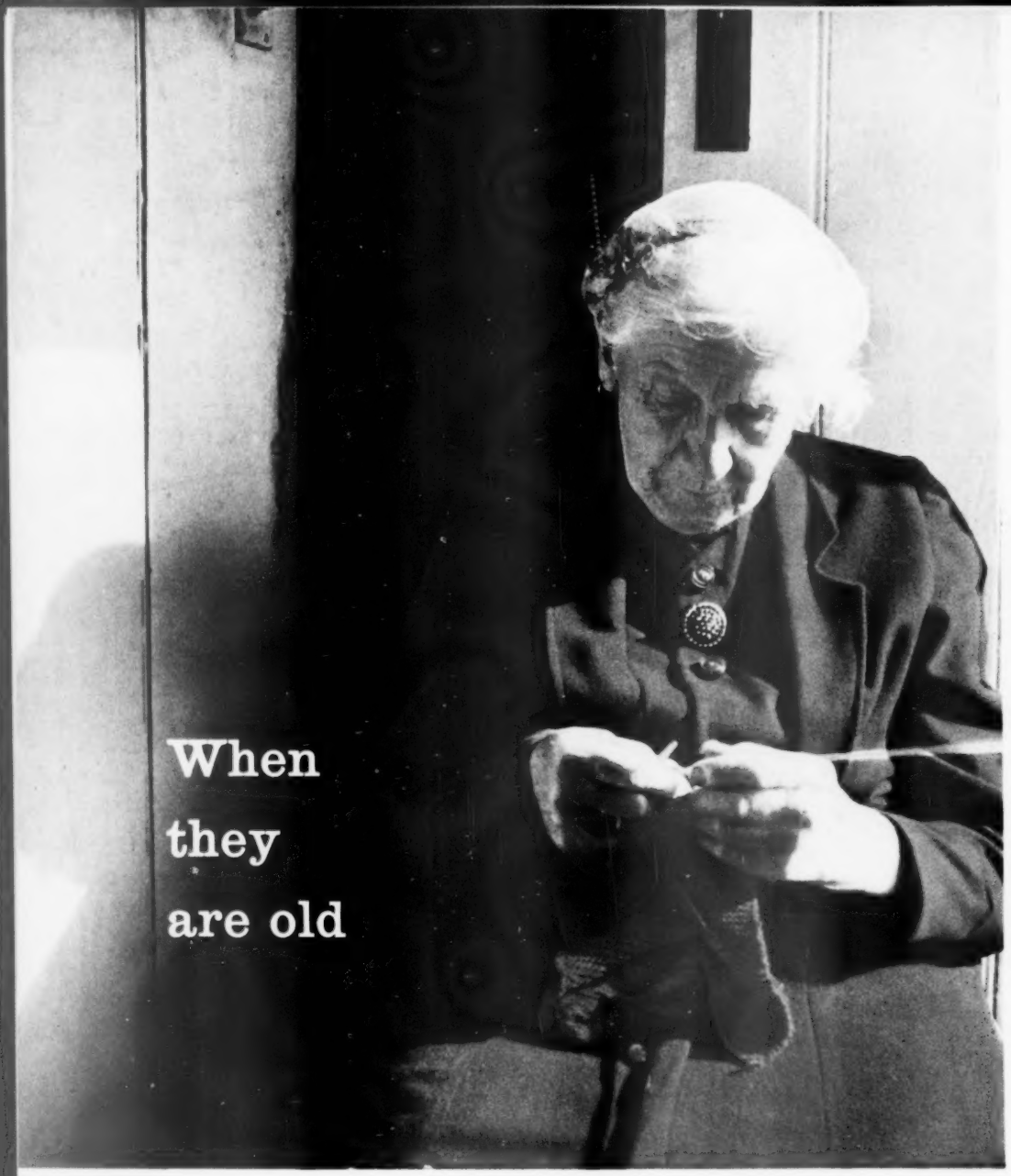

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